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Those named below have served as officers in this Section. This Section has included other subjects in the earlier years, as will be seen by the headings which denote the different Section titles. The names of the officers have been taken from the published records, which are deficient in some cases. It will be appreciated if any additional data are brought to the attention of the Secretary of the American Medical Association.

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PROCEEDINGS OF THE SECTION

First Day, June 13—Afternoon

The meeting was called to order by the chairman, Dr. Roger S. Morris, Cincinnati.

Dr. C. F. Hoover, Cleveland, was appointed on the Executive Committee in the absence of Dr. Charles Lyman Greene, St. Paul.

Dr. Walter V. Brem, Los Angeles, read a paper on "Blood Transfusion, With Special Reference to Blood Grouping." Discussed by Drs. Richard Lewisohn, New York; George R. Minot, Boston; F. G. Novy, Ann Arbor, Mich.; A. Jacobi, New York, and Walter V. Brem, Los Angeles.

Drs. Henry Sewall, William C. Mitchell and Cuthbert Powell, Denver, presented a paper on "Preliminary Observations on the Apparently Immunizing Behavior of the Mixed Serums of Immune and Hypersensitive Guinea-Pigs." Discussed by Drs. F. G. Novy, Ann Arbor, Mich.; Samuel J. Meltzer, New York, and Henry Sewall, Denver.

Dr. Downey L. Harris, St. Louis, read a paper on "Comparative Results in Antirabic Treatment with the Pasteur Method and with Desiccated Virus." Discussed by Drs. Samuel J. Meltzer, New York; William W. Tompkins, Charleston, W. Va., and Robert A. Peers, Colfax, Calif.

Wednesday, June 14—Morning

The following were appointed as a nominating committee: Drs. Nellis B. Foster, New York; Lawrence Litchfield, Pittsburgh, and Walter V. Brem, Los Angeles.

The following papers were read as a symposium on "Tests for Renal Function":

Dr. Nellis B. Foster, New York: "A Consideration of Types of Uremia."

Drs. Arthur F. Chace, New York, and Victor C. Myers, Albany, N. Y.: "The Value of Recent Laboratory Tests in the Diagnosis and Treatment of Nephritis, with Special

Drs. Herman O. Mosenthal and D. Sclater Lewis, Baltimore: "A Comparative Study of Tests for Renal Function." Reference to the Chemical Examination of the Blood."

These three papers were discussed by Drs. Henry A. Christian, Boston; Samuel J. Meltzer, New York; L. F. Barker, Baltimore; A. W. Hewlett, Ann Arbor, Mich.; H. J. Lehnhoff, Lincoln, Neb.; Nellis B. Foster, New York; Arthur F. Chace, New York, and Herman O. Mosenthal, Baltimore.

Dr. Edward C. Rosenow, Rochester, Minn., read a paper on "Lesions of the Nervous System Following Intravenous Injection of Bacteria." Discussed by Drs. Frank Billings, Chicago; Ernest Zueblin, Baltimore; Samuel J. Meltzer, New York; G. Canby Robinson, St. Louis; Henry A. Christian, Boston, and Edward C. Rosenow, Rochester, Minn.

Dr. Samuel Robinson, Rochester, Minn., read a paper on "Thoracic Disease—The Status of Surgical Therapy." Discussed by Drs. Willy Meyer, New York; F. T. Lord, Boston; Samuel J. Meltzer, New York, and Samuel Robinson, Rochester, Minn.

Wednesday, June 14—Afternoon

A joint meeting was held with the Section on Surgery, General and Abdominal. For a report of the proceedings, see the minutes of that section.

Thursday, June 15—Morning

The following officers were elected: chairman, Dr. Henry A. Christian, Boston; vice chairman, Dr. Douglas Vanderhoof, Richmond, Va.; secretary, Dr. James S. McLester, Birmingham, Ala.; delegate, Dr. Samuel J. Meltzer, New York; alternate, Dr. Herbert C. Moffitt, San Francisco.

Drs. Thomas McCrae and Elmer H. Funk, Philadelphia, presented a paper on "Localized Bronchiectasis Involving the Upper Portions of the Lung, with Report of Four Cases (Necropsy)." Discussed by Drs. F. T. Lord, Boston; Thomas McCrae, Philadelphia, and Elmer H. Funk, Philadelphia.

Dr. John E. Greiwe, Cincinnati, read a paper on "Premature Ventricular Systoles and Their Clinical Significance." Discussed by Dr. Charles F. Hoover, Cleveland, and Walter J. Wilson, Detroit.

The following papers were read as a symposium on "Disturbances of Cardiac Mechanism":

Dr. Albion W. Hewlett, Ann Arbor, Mich.: "The Significance of Pulse Form."

Dr. G. Canby Robinson, St. Louis: "The Relation of Changes in the Form of the Electrocardiogram to Functional Derangements of the Heart Muscle."

Dr. Francis W. Peabody, Boston: "Some Factors in the Production of Cardiac Dyspnea."

Dr. Augustus W. Crane, Kalamazoo, Mich.: "Roentgenograms: Polygraphic Strip Tracings of Heart Chambers by the Roentgen Ray."

These four papers were discussed by Drs. Frank N. Wilson, Ann Arbor, Mich.; S. Marx White, Minneapolis; Philip S. Roy, Washington, D. C.; Hugo A. Freund, Detroit; F. T. Lord, Boston; Albion W. Hewlett, Ann Arbor, Mich., and John E. Greiwe, Cincinnati.

Drs. Walter Hamburger, Harry Ginsburg and Isadore Tumpowsky, Chicago, presented a paper on "Mechanism of Hunger Pain in Chronic Ulcer." No discussion.

Dr. Willard J. Stone, Toledo, Ohio, read a paper on "Further Experiences with Carbohydrate Restriction in the Treatment of Hyperchlorhydria and Ulcer." Discussed by Drs. Samuel J. Meltzer, New York; M. H. Fussell, Philadelphia; Anthony Bassler, New York; J. W. Draper, New York; Isadore Tumpowsky, Chicago, and Willard J. Stone, Toledo.

Dr. Cabot Lull, Birmingham, Ala., read a paper on "Syphilis as a Probable Factor in Vague Stomach Disorders." No discussion.

Dr. H. L. McNeil, Galveston, Texas, read a paper on "Syphilis in the Southern Negro as Determined by One Thousand Wassermann and Luetin Reactions Done on Hospital Patients." Discussed by Drs. Frank Smithies, Chicago, and Fenton B. Turck, New York.

BLOOD TRANSFUSION

WITH SPECIAL REFERENCE TO GROUP TESTS *

WALTER V. BREM, M.D.
LOS ANGELES

Since Moss[1] published in 1910 his remarkable studies of iso-agglutinins and isohemolysins, we have been working continually with these interesting bodies, and have applied the principles established by him to the practical work of transferring blood to patients suffering from various conditions. The work of Moss was so accurate and complete that during six years we have never found in it a flaw, nor have we been able to add anything essential to it. Our only addition is that we have been able to modify the technic of blood grouping so that it can be done easily and accurately within a few moment's time, and in this we have but applied Moss' principles of blood grouping to a microscopic method. Moss found that all normal and pathologic bloods alike could be classified into four groups by agglutination tests of the serums against the corpuscles. These groups are:

Group 1 (10 per cent.): Serum does not agglutinate any corpuscles. Corpuscles agglutinated by the serums of Groups 2, 3 and 4.

Group 2 (40 per cent.): Serum agglutinates corpuscles of Groups 1 and 3, not 2 or 4. Corpuscles agglutinated by serums of Groups 3 and 4, not 1 or 2.

Group 3 (7 per cent.): Serum agglutinates corpuscles of Groups 1 and 2, not 3 or 4. Corpuscles agglutinated by serums of Groups 2 and 4, not 1 or 3.

Group 4 (43 per cent.): Serum agglutinates corpuscles of Groups 1, 2 and 3, not 4. Corpuscles not agglutinated by any serums.

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* From the Clinical Laboratory of Brem, Zeiler and Hill.

1. Moss, M. L.: Isoagglutinins and Isohemolysins, Bull. Johns Hopkins Hosp., 1910, xxi, 63.

It may be seen that no serum agglutinates corpuscles belonging to its own group, and furthermore, that if one has a known Group 2 or Group 3 blood, he can determine the group of any other blood by testing the known serum against the unknown corpuscles, and the unknown serum against the known corpuscles. As Moss thought, we have found that the group reactions of any one person appear to be permanent characteristics, inherited, and that they probably follow the mendelian law. In 1910, my associate, Dr. A. H. Zeiler, and I found that our bloods belonged to the reciprocal Groups 2 and 3, respectively, and in tests made many times during six years, there has been no change in the group reactions. We have been able, therefore, to use either one of our bloods in determining the groups of unknown bloods.

Moss found, further, that isohemolysins, when present, always followed the group reactions of iso-agglutinins, but that while iso-agglutinins are always present with isohemolysins, the contrary is not true, and that isohemolysins are not always present with iso-agglutinins. Isohemolysins cannot be used, therefore, in determining blood groups. The isohemolysins may even interfere with the group determination, for strong isohemolysins may break up the agglutinated corpuscles so rapidly that they may mask the agglutination reaction. This source of error must be guarded against, especially in using the microscopic method to be described. We ourselves were led once into error by the phenomenon, and the result of the transfusion was most alarming.

The possibility of such an error arising can be obviated by using the antihemolysin which Moss found constantly present in the serum of the blood whose corpuscles are hemolyzed by a serum belonging to another group. If a little of the antihemolytic serum is mixed with the preparation of corpuscles and serum to be tested, it will prevent hemolysis, and the agglutination will proceed without interference, as serums contain no antiagglutinins.

Another precaution that must be observed is that the known Group 2 or Group 3 blood which is used for determining the group of another blood must contain in the serum strong agglutinins. The strength or quantity of agglutinins varies in different serums even of the same group, and we were led into serious error on another occasion by using a known Group 2 blood, which was weak in agglutinins, for determining the group of a donor. The known Group 2 corpuscles were not agglutinated by the donor's serum, and the known Group 2 serum apparently did not affect the donor's corpuscles, that is, the donor apparently belonged to Group 2, which was the group desired for transfusion. The reaction which resulted in this instance, also, was most alarming. Afterward we regrouped the donor's blood with another Group 2 blood and found that the known Group 2 serum agglutinated the unknown corpuscles, and that the unknown serum did not agglutinate the known Group 2 corpuscles, that is, the donor's blood belonged to Group 1 and was unsuitable for the transfusion.

In view of these facts, the technic and rationale of the method of blood grouping which we use can be easily understood.

Let *II* represent a known blood belonging to Group 2, and *x* a blood the group of which must be determined. Five or 6 drops of *II* blood are collected in a small clean dry test tube or centrifuge tube, and 1 or 2 drops, according to the size of the drops, in another tube containing 1 c.c. of 1.5 per cent. sodium citrate in 0.9 per cent. salt solution, which gives one approximately a 5 per cent. suspension of corpuscles. The percentage does not have to be exact. The *x* blood is collected in the same way in two similar tubes. The bloods in the dry tubes are allowed to coagulate, the coagulum is loosened from the side of the tube with a platinum wire, and the tubes centrifugalized to separate the serum. Serum and corpuscles are now ready for the tests. Platinum loopfuls of serum and corpuscles are placed on coverslips, which are inverted over an ordinary cell slide rimmed with petrolatum. Two loopfuls of serum are used and one of corpuscle suspension. The slides are gently rolled from side to side to agitate the corpuscles in order to bring

them into contact with each other. Agglutination, if it occurs, takes place at room temperature within five minutes. It can usually be detected with the naked eye, showing as brick red particles, but should be examined, also, with the low power objective of the microscope. Rouleaux formation of red corpuscles must be differentiated from small clumps due to agglutination.

ILLUSTRATIONS OF GROUP DETERMINATIONS (THE FIGURES REFER TO LOOPFULS)

2 *II* serum + 1 *x* corpuscles = agglutination
2 *x* serum + 1 *II* corpuscles = 0

Group 2 serum agglutinates the corpuscles of Groups 1 and 3 only. But Group 3 serum agglutinates the corpuscles of Group 2, which does not happen in the foregoing test with *x* serum and *II* corpuscles. The *x* blood does not belong therefore, to Group 3, but must belong to Group 1.

2 *II* serum + 1 *x* corpuscles = agglutination
2 *x* serum + 1 *II* corpuscles = agglutination

Each serum agglutinates the other corpuscles, so the two bloods belong to the reciprocal Groups 2 and 3, that is, the *x* blood belongs to Group 3.

2 *II* serum + 1 *x* corpuscles = 0
2 *x* serum + 1 *II* corpuscles = agglutination

Group 2 serum does not agglutinate Group 2 or Group 4 corpuscles, while it does agglutinate the corpuscles of Groups 1 and 3. The *x* blood belongs, therefore, to Group 2 or Group 4. Which one is determined by testing *x* serum against *II* corpuscles, which it agglutinates. A serum does not agglutinate corpuscles belonging to its own group, so the *x* blood does not belong to Group 2, but must belong to Group 4, the serum of which does agglutinate Group 2 corpuscles.

2 *II* serum + 1 *x* corpuscles = 0
2 *x* serum + 1 *II* corpuscles = 0

The *x* blood belongs to the same group as the blood used for testing, Group 2.

COMMENT ON THE METHOD

This method of determining the group of an unknown blood requires not more than fifteen minutes after the bloods are obtained, and only small quantities of blood, such as can be obtained from a puncture of the finger tip, are necessary. The masking of agglutination by hemolysins is prevented by the serum, containing antihemolysin, that is present in the citrate-salt-

corpuscle mixture. This serum, if not present in sufficient quantity to prevent hemolysis, at least delays hemolysis so that agglutination is not masked. Neither the presence of this serum, nor the citrate interferes with agglutination, and hemolysins can be disregarded.

The assertion of some authors that hemolysins can occur without agglutinins, and that, therefore, a test for hemolysins as well as agglutinins must be made, is based, without doubt, on the fact that in the tests with washed corpuscles suspended in salt solution, hemolysis can cause such a rapid breaking up of clumps of corpuscles as to mask agglutination. In order to detect agglutinins in these bloods, the preparations must be watched with care microscopically during the first few minutes after the serum and corpuscles have been mixed. I have seen complete hemolysis of corpuscles in salt solution occur in the test tube within five minutes, leaving, of course, no trace of agglutination. But marked agglutination occurred immediately in the microscopic preparations, or in preparations which contained some of the serum of the blood to which the corpuscles belonged. The quantity of the antihemolytic serum necessary to prevent hemolysis probably varies widely according to the strength of the hemolytic serum. The hemolytic action of one serum was not inhibited by the presence in the test of 2.5 per cent. of the antihemolytic serum, but 11 per cent. partially inhibited hemolysis. One loopful of antihemolytic serum added to the test mixture of two loopfuls of serum and one of washed corpuscles (making a 25 per cent. solution of the antihemolytic serum) has always inhibited hemolysis, and it is a safe plan to introduce this element into the test.

The hemolysis with hemoglobinuria which has occurred from transfusions with ungrouped bloods is explained by the dilution of the antihemolysin in the donor's serum, the dilution being great enough to leave the introduced corpuscles unprotected or but partially protected. It is probable that hemolytic serum intro-

duced in a transfusion never causes hemolysis of the patient's corpuscles, for in such a case the hemolytic serum is diluted, while the antihemolytic elements of the patient's serum remain relatively concentrated. The agglutinins, also, may be diluted beyond the point of danger by the patient's serum. If, therefore, it is necessary in an emergency to give a patient blood belonging to a different group, the corpuscles should not be agglutinated or hemolyzed by the patient's serum, as pointed out by Ottenberg.[2] Bloods of Group 4 answer this requirement for all the other groups, and, fortunately, Group 4 is the most common group, Moss having found that 43 per cent. of all bloods belong to it.

TRANSFUSIONS

It is not within the scope of this paper to discuss the indications for transfusion, the results and the reactions. This ground has been covered recently in a thorough manner by Ottenberg and Libman,[3] and our observations, in the main, agree with theirs. We have given 191 transfusions — 165 of defibrinated blood, nine of 1 per cent. citrated blood, eleven of 0.2 per cent. citrated blood, and six of whole blood by the syringe-needle method. Our widest experience has been with pernicious anemia — eighty-two transfusions to twenty-four patients, one of whom received twenty transfusions. Our most successful transfusions have been in cases of secondary anemia due to hemorrhage, and preceding operations. We have had reactions in about 25 per cent. of the instances. These generally consisted in the ordinary chill and fever, and were usually mild. Severe reactions occurred four times after transfusions of 1 per cent. citrated blood (Weil[4]). The temperature of one patient reached

2. Ottenberg, Reuben: Studies in Isoagglutination, I, Transfusion and the Question of Intravascular Agglutination, Jour. Exper. Med., 1911, xiii, 425.

3. Ottenberg, R., and Libman, E.: Blood Transfusion; Indications; Results; General Management, Am. Jour. Med. Sc., 1915, cl, 36.

4. Weil, Richard: Sodium Citrate in the Transfusion of Blood, THE JOURNAL A. M. A., Jan. 30, 1915, p. 425.

106 F., and remained elevated for about a week. Two other patients died a few hours after, but it is fair to say that these patients were moribund at the time of transfusion. However, we feel that 1 per cent. citrated blood is toxic, is dangerous, and is unnecessary. Lewisohn's[5] method of giving 0.2 per cent. citrated blood seems safe, and this quantity of sodium citrate is sufficient to prevent clotting. Three anaphylactoid reactions occurred, two, at least, being in patients having active advanced tuberculosis. These are a study in themselves and will be discussed in a future paper.

The reactions which concern us chiefly at present are those associated with "incompatible bloods," that is, cases in which the donor's blood does not belong to the same group as the recipient's blood.

There were twelve such instances in our series. In seven instances the donor's serum was agglutinative for the recipient's corpuscles, but the recipient's serum was not agglutinative for the donor's corpuscles. There were no reactions suggestive of wrong grouping, though two of the patients had the ordinary chill and fever following. The absence of "group reactions" in the cases coincides with the view previously expressed that when agglutinative and hemolytic serum is introduced into a patient, the serum is so diluted by the patient's serum and the latter contains such an excessive quantity of antihemolysin that no "group reaction" should result. The reaction of recipients to donors in these seven instances was as follows:

Four Group 2 patients were given blood from Group 4 donors.

One Group 1 patient received three transfusions from Group 2 donors.

An eighth patient, belonging to Group 3, was given 100 c.c. of whole blood from her husband, who belonged to Group 2. The blood was transferred immediately with syringes while the patient was under an anesthetic. There

5. Lewisohn, R.: The Citrate Method of Blood Transfusion in Children, Am. Jour. Med. Sc., 1915, cl, 886.

was no reaction, but a "group reaction" might have been masked by the ether anesthetic. Each of these serums was agglutinative for the other corpuscles.

In the four remaining instances, the bloods bore the following relations:

Two Group 4 patients received Group 2 blood.
One Group 2 patient received Group 1 blood.
One Group 3 patient received Group 1 blood.

Three of these patients had violent reactions coming on immediately after the injection of only a small quantity, from 10 to 70 c.c., of blood. One of these had marked hemoglobinuria. The fourth patient had a mild reaction during the transfusion, which, however, was completed, 550 c.c. of blood being given. It was found later that this patient's serum was only weakly agglutinative to the corpuscles injected, and this fortunate fact probably explains why the reaction was mild. All of these patients recovered, and had no trouble with later transfusions.

An analysis of the causes of the transfusions of blood belonging to wrong groups shows that twice it was done because of emergency cases, three times because no Group 1 donor could be obtained for the patient who belonged to that rare group, and the other seven times it occurred through an error made in group testing, errors that can now be avoided. In none of the 179 instances of transfusions in which proper groups were used was there hemoglobinuria or "group reactions."

GROUP REACTIONS

These reactions are quite typical and come on quickly as a rule after the transfusion is begun, sometimes only 10 c.c. of blood being needed to precipitate the onset. There is a feeling of fulness in the head, suffusion of the face and eyes, precardial distress, dyspnea, coughing, backache, rapid and small pulse which may become imperceptible at the wrist, and sometimes complete loss of consciousness, and convulsions. Hemoglobinuria may occur. The shock is very much like the anaphylactoid shock, only, in our cases, the urticarial rash of the latter was absent. According to the views of Jobling and Petersen[6] and Bronfen-

6. Jobling, J. W., and Petersen, W.: Mechanism of Anaphylatoxin Formation, Jour. Exper. Med., 1914, xx, 37.

brenner[7] on tryptic shock, the conditions here are ideal for the anaphylactic phenomenon. The corpuscles introduced may be considered the antigen, and the hemolysin (which is an amboceptor-complement hemolysin) as the antibody. The union of antigen and antibody may cause the adsorption of antitrypsin, and the products of trypsin digestion of the patient's own serum may cause the shock.

CONCLUSION

The practical working out of our group tests and method of transfusions has proved most satisfactory. We have determined the groups of numerous donors and have made Wassermann tests on their bloods. Our laboratory keeps in touch with these donors, who are glad to give several hundred cubic centimeters of their blood for a small sum of money. They come to the laboratory, and, by the needle and vacuum flask method, we withdraw the quantity of blood desired, having first cocainized the skin over the vein. Some of these donors have been used many times during four years. They lose no time from work, the procedure is practically painless, they feel that the money is easily earned, and the patient is under no obligation to the donor. Having our donors classified and knowing their Wassermann tests are negative, we are in a position to give transfusions quickly. A group test of the patient's blood requires only a few minutes after the blood is obtained, and then we can summon the correct donor. The method is simple and easy for every one concerned, and the results, as far as I can judge from the literature, are as satisfactory as from other methods of transfusion. The defibrinated or citrated blood is injected intravenously through a needle without previous incision of the skin. The skin is cocainized at the time of injection.

7. Bronfenbrenner, J.: The Mechanism of the Abderhalden Reaction, Jour. Exper. Med., 1915, xxi, 221.

ABSTRACT OF DISCUSSION

DR. RICHARD LEWISOHN, New York: I agree thoroughly with Dr. Brem's remarks about the toxicity of Weil's dose, in fact I was the first one to show that citrate of soda mixed with blood at the 1 per cent. ratio is extremely toxic when used in large transfusions. The general applicability of citrate of soda for blood transfusions, and the perfect safety of its use is based entirely on the small dose (0.2 per cent.). I have used the method in seventy-five cases; 20 per cent. had a rise of temperature above 101 F., and 10 per cent. had a chill. The clinical effect of the transfusions was not impaired by these reactions. I wish to sound a note of warning against the storage of the blood, or against the transfer of citrated blood from house to house. I have used this method of transfer in two transfusions and had a severe reaction in both of them. After all we know very little about biologic changes in blood which is kept in storage.

DR. GEORGE R. MINOT, Boston: At the Massachusetts General Hospital we have made use of the groups for testing donors for transfusion. Our results are quite in accord with those of Dr. Brem. I have found the use of unwashed citrated suspensions of cells of advantage in the microscopic iso-agglutination tests. I have also made use of the fact, that given serum and cells of a known Group 2 or 3, one can determine to what group an individual belongs. Dr. Moss told me that recently he found that the individual's group is often not established at birth, but that it is established in 85 per cent. of children between 1 and 2 years of age, though it may not be established completely until 10 years of age or more. Thus in testing children's blood it is perhaps better to use a direct test between donor and patient rather than the group method.

DR. F. G. NOVY, Ann Arbor, Mich.: There is one thing that needs to be emphasized in view of the statement that the poisonous effects at times following the injection of serum resemble those of anaphylactic shock. I wish to make the statement even stronger and say that normal serum is always poisonous and that the symptoms do not merely resemble but actually are those of anaphylactic shock. We used to think that serum was harmless and that it could be injected as freely as water, that is, salt solution. Such, however, is not the case since simple animal experiments show that normal serums are toxic. The effects produced depend on the dose employed, and also on the method of preparing the serum. Thus, a serum made by defibrinating with beads is considerably more toxic than one prepared by simply whipping with a glass rod. As regards the use of whole blood, it should be realized that the same danger exists, and is even greater since whole blood may become, in a short

time, even more toxic than serum. Thus, to illustrate this statement, it may be said that 10 c.c. of blood drawn from a rabbit and injected intravenously into a guinea-pig, with the least possible delay, will produce little or no effect. On the other hand, if such blood is kept in the syringe for three minutes and is then injected, it will kill in a dose of 2 c.c. A typical, acute anaphylactic shock is the result. In other words, whole blood is more toxic the nearer it is to the coagulation stage. This toxicity has nothing to do with clot itself. The use of citrated serum, as pointed out, has its dangers which are more pronounced the longer it is kept. It can easily be shown that the incubation of a citrated serum results in the production of increased toxicity. That serum is something more than a harmless fluid should be recognized and not lost sight of in the future.

DR. ABRAHAM JACOBI, New York: Dr. Novy, when the serum is injected into the spinal canal is the effect as poisonous as when it is injected in the usual way?

DR. NOVY: I have had no experience in that line. My experiments have been made intravenously.

DR. WALTER V. BREM, Los Angeles: Dr. Lewisohn suggested that it might be a dangerous procedure to withdraw blood from a donor and carry it to another place for injection into the recipient; that some alteration in the blood might occur. We have done this in nearly all of our transfusions, and have not been able to attribute special reactions to it. We have transported the blood as far as seventy miles without reactions ensuing.

Dr. Novy said that serum and whole blood were deadly poison. I do not doubt that Dr. Novy can make them so by his physical methods of treating them, but these procedures do not appear to be reproduced in the technic of our transfusions; and the mild transfusion reactions that not infrequently do occur do not appear to interfere with the good results from the transfusion. It would seem, therefore, that these animal experiments of Dr. Novy do not weigh heavily against the results obtained in our method of transfusion of human beings, such transfusions having in themselves experimental value. However, Dr. Novy's work may throw light on some of the reactions and enable us to eliminate them.

I agree with Dr. Novy that the reactions I described as "group reactions" are true anaphylactic phenomena, but I felt that "anaphylactoid" would be the better word at present, for there is too great a tendency abroad to use loosely the term "anaphylaxis."

IMMUNITY CONFERRED BY THE TRANSFER OF IMMUNE AND OF MIXED IMMUNE AND SENSITIZED SERUMS

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We venture to present a few facts on an intricate subject, conscious that their full meaning and value must await the verdict of prolonged research.

In a recent investigation by two of us[1] it was found that when horse serum was dropped into the nose of a guinea-pig on alternate days, as few as four times, the animal became biologically modified in one of two opposite directions. A "toxic" injection of a large dose of serum given by the vein sixteen days after the last instillation could strongly shock or kill the guinea-pig. That is, the animal had become "sensitized" to the horse serum absorbed through the mucous membrane of the nose as if it had been given by subcutaneous injection. In certain animals, however, the toxic injection of horse serum not only did not kill, but produced scarcely noticeable symptoms of reaction.

Such a result would be attributed to incomplete absorption of the antigen were it not that a second large intravenous injection of serum, given two weeks after the first, was likewise frequently withstood.

In the work referred to it was found that the quality of the effect depended on the quantity of the serum

1. Sewall, Henry, and Powell, Cuthbert: On the Conditions and Characters of the Immunity Produced in Guinea-Pigs by Instillation of Horse Serum into the Nose, Jour. Exper. Med., 1916, xxiv, No. 1.

instilled. A dosage of 0.2 c.c. of horse serum generally produced fatal anaphylaxis, while a dose of 0.04 c.c. commonly conferred tolerance.

We could explain our results only on the hypothesis that the absorption of horse serum, according to dosage, initiated in the guinea-pig two opposite reactions, one of which was manifested by the anaphylactic state and the other by a condition of primary increased tolerance for the antigen. We further found that guinea-pigs prepared by a course of nasal instillations of serum, as compared with animals prepared by massive intraperitoneal injections, responded differently to a series of intravenous injections of horse serum. Animals given the preliminary treatments by the parenteral route, as is well known, tolerate continuously increased amounts of serum in spaced intravenous injections; but if a long resting period, say upward of 100 days, intervenes, there is more or less pronounced return toward hypersensitiveness.

When, on the contrary, guinea-pigs prepared by the nasal instillation of serum are submitted to a similar course of intravenous injections, tolerance for the antigen apparently increases with the length of the resting period, at least during the lapse of 125 days.

One of the fundamental data of immunology is the presence in the blood of an animal sensitized to a foreign serum of an anaphylactic antibody. When the serum of an animal sensitized to horse serum is injected into the peritoneal cavity of a normal guinea-pig, this creature itself passively acquires hypersensitiveness to horse serum.

In the present work we undertook to solve the following apparently simple problem: Given two guinea-pigs, one of which is hypersensitive to horse serum and the other resistant to it, does the serum of the latter animal contain anything which may neutralize or modify the admitted anaphylactic effects induced by the serum of the hypersensitive animal? An affirma-

tive result would suggest the hypothesis of an "immune body" functionally opposite in action to that concerned in anaphylactic reactions.

The meager results thus far obtained are presented now only because it has become necessary to postpone indefinitely continuation of the work. This survey has employed seventy-two animals in twelve series of experiments. The crucial purpose of each group of experiments was to obtain the blood serum of two guinea-pigs, one of which was highly resistant and the other highly sensitive to the intravenous injection of horse serum. The donor pigs were bled directly into tubes in which the serum was separated by centrifugation within half an hour. The serums from the two animals were injected at once, separately and mixed in various proportions, into the peritoneal cavities of normal guinea-pigs having an average weight of 300 gm. The mixed serums were incubated together for from fifteen to forty minutes, either at room temperature or at 37 C. (98.6 F.) before injection. After a resting period of from two to three days, these pigs received an intravenous injection of 0.25 c.c. of horse serum and, in case of survival, the injection was repeated at intervals of fourteen days or more.

Our usual method of procedure was to inject 3 c.c. of the serum from sensitive and resistant animals, respectively, into two normal guinea-pigs, and then mixtures of serums in the proportions 3 + 1, 1 + 3 and 1 + 1 into other normal animals. Our first technical difficulty was encountered in the preparation of animals with such a high blood content of anaphylactic antibody that a normal pig receiving 3 c.c. of the serum would succumb in forty-eight hours to the intravenous injection of 0.25 c.c. of horse serum. In most cases the recipient pig was only shocked with the first intravenous injection, succumbing to the second. The usual preparatory treatment of pigs designed to develop anaphylactic antibodies consisted in from three to four

daily intraperitoneal injections of from 2 to 5 c.c. of horse serum, the pigs being bled from fourteen to forty-eight days later.

It is obvious that the degree of sensitization acquired by the normal pigs, as a result of the intraperitoneal injection of sensitized serum, would be manifested as an anaphylactic response to the first intravenous injection of horse serum.

Eight of the forty-six normal animals receiving the serum of treated pigs died with the first intravenous injection of horse serum. Three showed no definite reaction, one of these succumbing to the second intravenous injection. The remainder showed a varying degree of reaction.

It is further obvious that the first intravenous injection of 0.25 c.c. of horse serum would, under ordinary conditions, strongly sensitize the guinea-pigs so that they would invariably succumb to a second injection of a like amount repeated after fourteen days or longer.

Our experiments show, however, that eleven of the forty-six pigs receiving serum of the treated animals withstood the second intravenous injection, and seven withstood three or more such injections, none of these, in fact, dying under treatment. The guinea-pigs used as donors of serum may be divided into two general classes. Those of the first class had been treated by the instillation of horse serum into the nose, but did not receive thereafter the usual intravenous injection of this serum. Half of these animals were instilled with what we call "protective" doses of 0.04 c.c. of horse serum, and half with "sensitizing" doses of 0.2 c.c. of the serum. From the results of parallel experiments it was assumed that the animals instilled with the smaller dosage would have withstood an intravenous injection of 0.25 c.c. of horse serum in sixteen days, and that those instilled with the larger dosage would have succumbed to such an injection. More ample experience has shown that this sharp bio-

logic distinction between animals according to the amount of antigen which they have received cannot always be predicated; nevertheless it is obvious that remarkable and specific properties may be acquired by the serum of guinea-pigs treated only by instillation of horse serum, without subsequent reinforcement with intravenous injection. This is shown in Table 1.

The letter L in the table signifies that the guinea-pig survived its intravenous injection with scarcely perceptible reaction; the number of + signs indicates degrees in severity of anaphylactic shock.

TABLE 1.—EXPERIMENTS WITH SERUM OF GUINEA-PIGS TREATED ONLY BY INSTILLATION OF HORSE SERUM

Donor Pigs†	Normal Pigs	Serum Intraperitoneally, C.c.	Results of Intravenous Injection of Horse Serum*					
			0.25 C.c.				0.38 C.c.	
			First, 48 Hrs. After Intraperitoneal	Second, 15 Days After First Intravenous	Third, 14 Days After Second Intravenous	Fourth, 17 Days After Third Intravenous	Fifth, 12 Days After Fourth Intravenous	Sixth, 59 Days After Fifth Intravenous
A	1	0.75	L	D				
A	2	4	L ++	D				
B	3	0.5	L +	D				
B	4	3.25	L +++	D				
A & B	5	A, 0.75 B, 2	L +	L +++	++++	L +++	L +	L +
A & B	6	A, 2 B, 0.5	L +	L +++	L+++	L +	L	L

* In this and the following tables, D means "dies"; L means "lives after very slight reaction"; L ++++ means "very severe reaction."

† Preparation of donor pigs: A, immune; received six nasal instillations of 0.04 c.c. horse serum, alternate days; B, sensitive; like treatment with 0.2 c.c. horse serum. Both bled after 21 days.

It will be seen in the third column that every pig was to a degree sensitized by the intraperitoneal injection of serum from the donor animals. In the fourth column we see that pigs Nos. 5 and 6, which had received mixtures of serum from donors A and B (the mixtures having stood at room temperature for about thirteen minutes) survived the second intravenous injection, and repetitions of the same at various intervals and with increasing dosage.

We defer speculation as to the meaning of these facts until the general discussion at the close of this article. Suffice it now to postulate that the recipient Guinea-Pigs 5 and 6 have acquired an active immunity. One hundred and nineteen days elapsed between the intraperitoneal injection of immune serum and the last intravenous injection of horse serum. During this time six injections of horse serum were given and, in spite of the increase in the amount of antigen, the immunity of the pigs was progressively strengthened after the third treatment.

TABLE 2.—EXPERIMENTS WITH SERUM OF GUINEA-PIGS HIGHLY IMMUNIZED AGAINST HORSE SERUM

Donor Pigs*	Normal Pigs	Serum Intraperitoneally, C.c.	Results of Intravenous Injections of 0.25 C.c. Horse Serum			
			First, 47 Hours After Intraperitoneal	Second, 19 Days After First Intravenous	Third, 16 Days After Second Intravenous	Fourth, 45 Days After Third Intravenous
A	1	3	L	L	L +	L ++
B	2	3	D			
A & B	3	A, 1 B, 1	L	L ++	L +++	L ++

* Donor pigs treated by a course of nasal instillations and later by intravenous injections of horse serum. A was bled 19 days after last intravenous of 0.75 c.c. horse serum. B was bled 17 days after intravenous of 0.88 c.c. horse serum.

In numerous experiments which we have performed on pigs born of immune and sensitive mothers, never have we seen one survive the second intravenous injection of horse serum. It might be maintained, of course, that our Pigs 5 and 6 acquired their active immunity from the small residue of horse serum remaining free in the circulation of the donors A and B, but, as will be seen shortly, such an explanation is scarcely tenable. Nevertheless, this interpretation of the results is perhaps supported by the data conveyed in Table 2.

In this experiment both donor pigs were highly immunized against horse serum. After six nasal instil-

lations of 0.04 c.c. of horse serum, each withstood, with scarcely perceptible reaction, the intravenous injection of 0.38 c.c. of horse serum after sixteen days. Sixteen days later a similar injection was borne with moderate reaction. Sixty-seven days later A reacted moderately to an intravenous injection of horse serum increased to 0.75 c.c., and in sixty-nine days B responded in the same way to an intravenous injection of 0.88 c.c. of horse serum. These pigs were bled at the same time, A nineteen days after receiving 0.75 c.c. of horse serum, and B seventeen days after receiving 0.88 c.c. of the serum. It is seen that the normal recipient of B's serum died with the first intravenous injection, while the other two recipients were immunized. The mixed serums of A and B were incubated at 37 C. for twelve minutes.

It is worth while noting that the immunity conferred on normal guinea-pigs by this method usually develops more slowly and less perfectly than in animals immunized after a course of nasal instillations of horse serum.[1]

Our experiments substantiate the opinion that the effect of serum transferred by intraperitoneal injection to a normal animal depends not only on its composition but also on the quantity injected and, when mixtures of the serum are used, on the relative amounts of "immune" and "sensitive" serum employed.

Our experiments are far too limited in number to establish the quantitative relations of the variables in this supremely practical problem. Nevertheless, certion conclusions seem to be indicated, thus: mixtures of immune and sensitive serums appear to be more potent to confer immunity on the normal guinea-pig than immune serum alone, and those mixtures which contain the smaller proportion of immune serum are apparently most effective in this direction.

Mixtures of the serum of two hypersensitive donors, on the other hand, appear to be quantitatively more

potent to induce the anaphylactic state in normal pigs than either serum alone.

In Table 3 the results of three series of experiments are condensed. In the first, the immune Pig A, after a course of nasal instillations with horse serum, had received at long intervals five intravenous injections of horse serum, the last, amounting to 0.75 c.c., being

TABLE 3.—RESULTS OF THREE SERIES OF EXPERIMENTS

Donor Pigs*	Normal Pigs	Mixed Serum Intraperitoneally, C.c.	Results of Intravenous Injections of 0.25 C.c. Horse Serum				
			First, 62 Hours After Intraperitoneal	Second, 14 Days After First Intravenous	Third, 13 Days After Second Intravenous	Fourth, 14 Days After Third Intravenous	Fifth, 33 Days After Fourth Intravenous
A & B	1	A, 2.5 B, 1.5	L +	D			
A & B	2	A, 1.5 B, 2.5	L ++	L +++	L +++	L +	L
		Separate and Mixed Serums	First, 87 Hours After Intraperitoneal	Second, 15 Days After First Intravenous	Third, 13 Days After Second Intravenous	Fourth, 36 Days After Third Intravenous	
C	1	3	L	L ++	L +	L	
D	2	3	D				
C & D	3	C, 3 D, 1	L +	D			
C & D	4	C, 1 D, 3	L ++	D			
		Separate and Mixed Serums	First, 87 Hours After Intraperitoneal	Second, 14 Days After First Intravenous	Third, 42 Days After Second Intravenous		
E	1	5	L +	L +++	D		
F	2	2	L ++	D			
E & F	3	E, 2 F, 2	L +	L ++	D		
E & F	4	E, 1 F, 2	L +	L ++	L +++		

* Preparation of donor pigs: A, immune pig; 6 nasal instillations, 0.2 c.c. horse serum followed by 5 intravenous injections in +5 months; last intravenous of 0.75 c.c. horse serum given 116 days before bleeding. B, sensitized pig; 4 intraperitoneal injections of from 2 to 5 c.c. horse serum daily; bled 25 days after last intraperitoneal. C, immune pig; 4 nasal instillations of 0.2 c.c. horse serum followed by 3 intravenous injections of horse serum in 51 days; last intravenous of 0.5 c.c. horse serum given 108 days before bleeding. D, sensitized pig; prepared like B, but bled 41 days after last intraperitoneal. E, immune pig; prepared by 12 daily instillations of 0.02 c.c. horse serum followed by 2 intravenous injections of horse serum within 3 weeks; last intravenous of 0.33 c.c. horse serum 107 days before bleeding. F, sensitized pig; three intraperitoneal injections of horse serum, from 1 to 4 c.c., daily; bled 17 days after last intraperitoneal.

given 116 days before the pig was bled. The animal was a female, and offspring born to it late in the treatment were completely refractory to subcutaneous injection of 0.1 c.c. of horse serum, while offspring of a sensitive mother succumbed to such an injection. Pig B was bled twenty-five days after its course of intraperitoneal injections; its serum, no doubt, would have been richer in anaphylactic antibodies had a longer interval elapsed. It is noticed that a stronger protection is afforded by the serum mixture containing the smaller amount of "immune" serum A. The same result is noted in Pig 4 of the third experiment. In the second experiment 3 c.c. of the serum of the sensitive Pig D contained enough anaphylactic antibodies to make the normal Pig 2 fatally sensitive to an intravenous injection of horse serum. Although the serum of the immune Pig C was rich enough in protective substance to protect Pig 1 against a series of intravenous injections of horse serum, it could only partly inhibit the fatal effect of the serum of D when mixed with it.

After it had been determined that immune serum and mixtures of immune and sensitized serum inoculated into normal guinea-pigs could protect them against anaphylactic death following intravenous injection of the antigen, it was obviously desirable to determine whether animals already hypersensitive to horse serum could be desensitized by similar treatment. A considerable number of experiments were performed in which guinea-pigs, sensitized to horse serum by subcutaneous injection, were given intraperitoneal injections of from 3 to 5 c.c. or more of serum and its mixtures, which probably would have protected normal animals against anaphylaxis. Each recipient pig was treated by an intravenous injection of horse serum in from three to seven days after the intraperitoneal injection, and each promptly died. We conclude that *prophylaxis* and *cure* of sensitization are practically

independent problems. A useful discussion of the essential differences between prophylactic and therapeutic vaccination has been given by Theobald Smith.[2]

COMMENTS

The present work must be considered in the light of facts announced in the previous article,[1] of which it is a continuation.

We are strengthened in the opinion expressed a year ago[3] that two different reaction bodies are formed in a normal animal when a foreign protein is introduced into its circulation. One of these is the anaphylactic antibody familiar to literature. The other is a protective antibody which averts the changes which result in anaphylactic shock. These antibodies probably always exist together in the circulation but, according to circumstances, in very different proportion. In the donor pigs which we have termed "sensitive" the anaphylactic antibody greatly predominates, while in the "immune" pigs the protective antibody is more or less pure. It is characteristic of the metabolism set up by the repeated absorption of very small quantities of horse serum by the nose that it results in the preponderant formation of the protective antibody. In an important research by Gurd,[4] conclusions are expressed which agree, in parts, exactly with our own:

> The experiments . . . are interpreted by the author as proving the presence, in the circulating blood of immune animals, of bodies which are potent to induce the hypersensitive state when introduced into normal animals and also of bodies which if injected in sufficient quantities are able to render normal animals immune.

We have shown that our "immune" serum, that presumably surcharged with protective antibodies, is alone

2. Smith, Theobald: Boston Med. and Surg. Jour., 1910, clxiii, 275.
3. Sewall, Henry and Powell, Cuthbert: Studies on the Relations of the Hypersusceptibility and Insusceptibility Induced in Guinea-Pigs by the Instillation of Horse Serum into the Nose, Arch. Int. Med., October, 1915, p. 605.
4. Gurd, F. B.: Jour. Med. Research, 1914, xxxi, 205.

capable of protecting normal guinea-pigs against a series of inoculations of horse serum, and that mixtures of "immune" and anaphylactic serums appear to be still more potent in this direction.

Considerable evidence has been developed, both from laboratory and clinical fields, which supports the view that a disease-producing organism or substance when combined with certain contents of immune serum has a peculiarly vaccinating or even curative effect.[5] Theobald Smith[6] seven years ago suggested the employment of mixtures of toxin-antitoxin in the prophylaxis of diphtheria. The more recent use of "sensitized" vaccines is evidently founded on the same principle.

A rich experience has been accumulated by students of hog cholera.[7] Prophylaxis against this disease may be secured by the subcutaneous inoculation of normal animals with "hyperimmune" serum, that is, serum from immune hogs that have withstood inoculation with actively infected blood. This treatment is not curative of the disease, and its protective power disappears after a few weeks. Prophylaxis by the "simultaneous" method is much more effective. According to this plan, a considerable quantity of hyperimmune serum is injected under the skin on one side of the animal, and a small amount of virulent blood is injected on the other side. The protection conferred is said to last throughout life, and hogs actually sick with the disease are cured in a considerable proportion of cases. Duval and Couret[8] have recently reported highly successful vaccination with "desiccated, sensitized hog cholera virus." They incubate the diseased tissues with hyperimmune serum, then dry and reduce them to a powder which is found effective for prophylaxis in exceedingly small amounts.

5. Wood, F. C., in Forchheimer's Therapeusis of Internal Diseases, 1914, i, 125.
6. Smith, Theobald: Jour. Exper. Med., 1909, xi, 241.
7. Dorset, M.; McBryde, C. N., and Niles, W. B.: Bull. 102, Bur. An. Ind., U. S. Dept. Agric., 1908. Dorset, M.: Farmers' Bull. 379, U. S. Dept. Agric., 1909.
8. Duval, C. W., and Couret, M. J.: Read before the Association of American Physicians, May 11, 1916.

We venture to offer the following explanation of the facts presented: The protective antibodies of our immune pigs when injected into normal animals combine with cells and initiate in them the tendency to produce similar antibodies under appropriate stimulation. Such stimulation is found in the antigen contained in horse serum. The result of such injection is a response of the body cells by which they produce such excess of protective over anaphylactic antibodies that repeated injections of horse serum are withstood. The evidence is that the effect of the protective antibody in directing the tissue metabolism is greatly enhanced by the presence in certain proportion of anaphylactic antibodies as found in the mixed serums. This is seen in Table 1. The rôle, then, of these reaction bodies injected into the normal animal is to modify cellular irritability in a manner to lead to the speedy and preponderant formation of "protective" antibodies under the stimulus of the antigen, and thus initiate the course of active immunity. The final status of the irritability of a living cell is determined, not only by the kind and amount of stimulating material invading it, but also by the metabolic predisposition of the cell at the moment of contact.

SUMMARY AND CONCLUSION

Our work was undertaken with the design of discovering whether the blood serum of guinea-pigs rendered immune to considerable intravenous injections of horse serum by a preceding course of nasal instillation of the serum has a different biologic effect from the serum of highly sensitive animals, when injected intraperitoneally into normal guinea-pigs. We have found that the serum of animals which we call immune can confer on normal guinea-pigs a resistance against a long succession of intravenous injections of the same antigen. It is also probable that mixtures of immune and sensitive serums in certain proportions give still greater protective effects. Notwithstanding the

numerical inadequacy of these experiments, we believe that, taken in connection with the broader research,[1] they justify the following tentative conclusion: A foreign protein injected into a normal animal sets up reactive processes leading to the formation, in this field, of two antibodies having opposite characters; one tends to induce, and the other to avert, the establishment of the anaphylactic state.

Serum containing an excess of the anaphylactic antibody, when transferred to normal animals, renders them, as is well known, passively anaphylactic. Serum containing a sufficient excess of the "protective" antibody, when transferred to normal animals, initiates in them the phenomena of active immunity. Mixtures of the two types of serum seem still more effective in conferring immunity.

The metabolism of the body cells is specifically modified by combination with these antibodies in such a way as to give rise to hypersensitization on the one hand or to active immunity on the other.

If our interpretation of these results is correct, it is evident that new definitions must be given for "immune" serums.

ABSTRACT OF DISCUSSION

Dr. F. G. Novy, Ann Arbor, Mich.: Dr. Sewall in his results on the treatment of anaphylactic shock has described a protective action. It seems to me immunity begins with the shock itself. As to the nature of anaphylaxis: We have been accustomed to look on the chemical changes in the body as the most important feature. I am certain that it will be found that these changes are purely physical from beginning to end and that there is no chemistry connected with it.

Dr. S. J. Meltzer, New York City: Dr. Sewall is possibly the first one to test the effect of serum not by its action in anaphylactic shock but by its action when it did not kill and later when it protected. He discovered that when subminimal doses were used it was protective. But all such findings must be confirmed before they can be accepted as facts. It is very important to use the serum in small doses by his method. Nobody will object to the use of serum to protect them from infections or against possible anaphylactic shock. It has been found that guinea-pigs may be made either hypersensi-

tive or insensitive to the action of horse serum following the placing of it in the nose and not in the stomach. It might be a good plan to give it by the stomach if the stomach is not full.

DR. HENRY SEWALL, Denver: As to taking the serum by way of the mouth, in a few cases in which I have tried it the results have been negative. The mucous membrane of the mouth absorbs any foreign protein slowly. Again, if it is introduced into the stomach by means of a tube certain errors enter into it and one may lacerate the epithelium.

COMPARATIVE RESULTS IN ANTIRABIC TREATMENT

WITH THE PASTEUR METHOD AND WITH DESICCATED VIRUS

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ST. LOUIS

Pasteur's method for antirabic treatment stands as such an imperishable landmark of experimental medicine that one hesitates to point out even one or two minor defects. But the fact is that nearly all who now prepare the virus for treatment, including the Pasteur Institute, have made changes in the original method of preparation. In the original method Pasteur found that the serial passage of rabies virus from rabbit to rabbit by subdural inoculation resulted in a steady shortening of the incubation period until it becomes stationary or fixed, with an incubation period of six days. The spinal cords of these rabbits gradually lose their infectivity if dried over potassium hydroxid. When the temperature is kept at 23 C., the cords are not infective after the ninth day.

Pasteur's method of treatment began with the injection of 1 cm. of cord dried for fourteen days, followed, day by day, for eighteen to twenty-one days, with cord of increasing infectivity, the two-day cord being the most infective which he felt could be used without infecting the patient. The effect of these injections is that in the course of three weeks immune bodies appear in the blood; and those patients survive in whom the incubation period of the infection is

longer than the time required for the establishment of an active immunity. This required time is from fifteen to twenty days after the completion of the treatment. The success of the treatment depends, therefore, on the fortunate circumstances that in man the incubation period of rabies is seldom less than three or four weeks and is usually about seven weeks. Pasteur regarded as complete failures only those patients who developed hydrophobia later than fifteen days after the completion of the treatment.

The preparation of the cords according to Pasteur's scheme requires the daily inoculation of one or more rabbits and the removal of the cords. It is therefore expensive and demands facilities which are to be found only in large, well-equipped laboratories. Modifications of the method have had for their object the establishment of an immunity which would appear earlier and be greater than that afforded by the Pasteur treatment. This has been sought for by the injection of virus of greater infectivity; by other methods for altering the infectivity of the virus, as, for example, heat, chemicals, dilution, dialyzing; by the simultaneous injection of serum, or sensitized vaccine.

Of the various modifications adopted, the earliest was proposed by Högyes.[1] This method is based on the fact that Pasteur's attenuation of cords by drying resulted only in a numerical destruction of the organisms. Högyes therefore devised a scheme of diluting fresh virus and injecting increasing quantities from day to day. The use of this scheme has been followed by excellent results. Ferran advocated and used small quantities of emulsified fresh cord. Proescher injects a relatively thick emulsion of fresh brain, and gives fewer injections. Calmette introduced the use of glycerol for preserving the cords. Fermi kills the organism by emulsifying the cord in 1 per cent. phenol (carbolic acid) and injects this noninfective

1. Högyes: Lyssa in Nothnagles Spez. Path. u. Therap., Wien, 1897.

material. He claims his results are better than can be attained with the Pasteur method. Marie,[2] in the Pasteur Institute, gives a sensitized virus which has been acted on by antirabic serum. His results are better than those obtained in the Institute before the adoption of this modification. Excellent results have followed the use of virus dialyzed according to the method proposed by Cummings.[3]

The modification of the Pasteur method which I wish to describe now is founded on Shackell's[4] very original investigations on the effect of desiccation in vacuo at a low temperature. The earlier experiments are recorded in a joint article with Shackell.[4] This method has for its object the preservation of fixed virus, in order that it may be prepared in quantity and be always available for treatment. By using both brain and cord, enough material is obtainable for thirty complete treatments with the virus from a single rabbit; and since the material can be stored until needed, there is no waste and no unnecessary work is required of the laboratory staff during periods when patients are lacking or very few. Furthermore, with this product, treatment may be administered in less than half the number of days required by the original method.

The preparation of the material is as follows: Brain and cord, stripped of pia and blood vessels, are ground in a mortar into a homogeneous, thick, paste-like mass; carbon dioxid snow, collected from a tank into a sterile cloth, is added to the paste until freezing is complete and until further grinding reduces the mass to a fine powder. This powder is transferred quickly to a cold beaker and placed in a Schibler's jar which has been submerged in a mixture of salt and ice (—18 C.). In the upper part of the jar is a beaker of concentrated sulphuric acid. A vacuum of less

2. Marie: L'etude experimentale de la rage, Paris, 1909.
3. Cummings: Jour. Infect. Dis., 1914, xiv, No. 1.
4. Shackell: Am. Jour. Physiol., 1909, xxiv, 325.

than 2 mm. is produced and the powdered brain is kept at —18 C. in the salt and ice until desiccation is complete. A single brain and cord will be completely dehydrated in from thirty-six to forty-eight hours. A more detailed description of the technic may be found in the published papers relating to this method.[5] If the brain and cord have been thoroughly ground, completely frozen and absolutely dried at a temperature not above —18 C., the resulting powder will be almost as infective as the fresh untreated brain and cord. When kept in vacuo at 0 C. there is no appreciable loss in infectivity for several months. When kept in an ice box (8 to 10 C.) for 500 days this powder is five times as infective as an equal quantity by weight of Pasteur's cord that has dried five days.[6]

Harvey and McKendrick[7] have shown that when cords are dried slowly over potassium hydroxid the loss of infectivity is proportionate to the loss of water. They conclude that the small amount of water remaining in the cord after the ninth day is insufficient to keep the rabies organisms alive. Vansteenbergh[8] had already succeeded, some years before our experiments, in preserving the infectivity of rabies virus by drying this very rapidly in vacuo. In his experiments the material was spread out in a very thin layer and the vacuum produced very quickly at room temperature. The dried powder retained its infectivity for some months if kept in the dark, free from moisture; but the amount of infectivity so preserved was very small. Our explanation of the apparently contradictory results of these two methods of dehydration is that in slow dehydration the salts and other soluble materials in the cells of the brain and cord become more and more concentrated until a point is reached at which this concentration becomes

5. Harris: Jour. Infect. Dis., 1912, x, 369; ibid., xi, 397; ibid., 1913, xiii, 155; ibid., Ann. de l'Inst. Pasteur, 1912, xxvi, 372.
6. Harris and Shackell: Jour. Infect. Dis., 1911, viii, 47.
7. Harvey and McKendrick: Theory and Practice of Antirabic Immunity, Calcutta, 1907.
8. Vansteenbergh: Compt. rend. Soc. de biol., 1903, lv, 1046.

sufficiently toxic to kill the enclosed organisms of rabies by direct chemical action. In the brain and cord dried over potassium hydroxid the loss of infectivity is proportional to the resultant concentration of the soluble substance. Vansteenbergh's partial success in desiccation in vacuo is due to the rapidity of the dehydration and partial avoidance of too great concentration. If the cord and brain are frozen and then desiccated, cell after cell is deprived of its ice, molecule by molecule, by volatilization; and, depending on the degree of freezing, there is therefore little or no possible concentration of salts or other soluble products. So long as the dried brain is kept dry its infectivity alters very slowly; but if this powder, which is hydroscopic, is exposed to air, water is absorbed, deliquescence occurs; chemical action begins, and all the infectivity is quickly lost. The amount of infectivity remaining after vacuum desiccation depends on the degree to which the material is kept frozen during the extraction. The preservation of infectivity afterward depends on its absolute freedom from moisture.

Numerous tests made with various lots of our desiccated virus showed the loss of infectivity to be constant and uniform, and demonstrated the value of the method as a means of preserving the virus. Experiments were therefore begun on dogs and rabbits to determine its value in immunization, and these showed conclusively that the material could be used with great advantage in antirabic immunization of rabbits and dogs. The results have recently been confirmed by Poor, Jelnick and Gibson in the New York City Health Department laboratories. In a personal communication, Dr. Poor has kindly furnished the following protocols of some of the work carried on to determine the comparative value of various modifications of the Pasteur methods with that of the original.

EXPERIMENT 1.—Pasteur's cord and Harris' desiccated virus were used. The animals in each series were treated ten days. The virus was sent from Dr. Harris' laboratory; age of virus

two years. The minimal infective dose was supposed to be 0.1 mg. for the first day's treatment and 0.01 mg. for that of succeeding days, but according to our tests they were much lower. The exact minimal infective dose was not determined by us. The animals treated with this virus received the following doses, which constitutes the ordinary scheme proposed by Dr. Harris for treatment of human beings:

Day	Units
1st	500
2d	1,000
3d	1,500
4th	2,000
5th	3,000
6th	3,000
7th	3,000
8th	3,000
9th	3,000
10th	3,000

Unless otherwise stated this scheme was followed in all subsequent experiments. The rabbits in the Pasteur series received the full doses given to human patients on the first ten days of the regular course of Pasteur treatment.

Forty-three days after the end of treatment the animals were infected intracerebrally with the following dilutions of mixed virus:

One to 8,000 Harris' Virus:
Rabbit 1, discharged after seven weeks.
Pasteur Virus:
Rabbit 1, paralyzed in thirteen days.
Rabbit 2, paralyzed in seven days.
Controls:
Rabbit 1, paralyzed in seven days.
Rabbit 2, paralyzed in seven days.
One to 4,000 Harris' Virus:
Rabbit 1, remained well for thirty-two days, then developed snuffles and died.
Rabbit 2, discharged after seven weeks.
Pasteur Virus:
Rabbit 1, paralyzed in seven days.
Rabbit 2, paralyzed in six days.
Control:
Rabbit 1, paralyzed in seven days.
One to 1,000:
Rabbits of all series showed beginning symptoms of rabies in six days.

EXPERIMENT 2.—Pasteur and Harris methods were used, and all animals were treated eleven days. Harris' virus was sent from Dr. Harris' laboratory. The minimal infective dose for the first day's treatment was 0.1 mg.; that of virus for

succeeding days 1/80 mg. The animals were infected the day after the last injection with the following dilutions of fixed virus:

1 to 12,000

Control: Rabbit 1, paralyzed in ten days; Rabbit 2, paralyzed in seven days.

Pasteur virus and Harris' virus: Rabbit 1, discharged in forty days; Rabbit 2, discharged in forty days.

1 to 8,000

Control: Rabbit 1, paralyzed in seven days; Rabbit 2, paralyzed in eight days.

Pasteur virus: Rabbit 1, paralyzed in eight days; Rabbit 2, paralyzed in eight days.

Harris' virus: Rabbit 1, discharged in forty days; Rabbit 2, discharged in forty days.

1 to 4,000

Control: Rabbit 1, paralyzed in eight days.

Pasteur virus: Rabbit 1, paralyzed in eight days.

Harris' virus: Rabbit 1, discharged in forty days.

EXPERIMENT 3.—Harris' series, treated ten days; Pasteur series treated twenty-one days, starting eleven days ahead of the Harris series.

Harris' virus: Virus used for the first day's treatment made by Eli Lilly & Co.; minimal infective dose 0.1 mg. That for the succeeding days, made by us; minimal infective dose 1/200 mg.; virus one month old. On the day after the last injection all animals infected with the following dilutions of fixed virus:

1 to 8,000

Control: Rabbit 1, paralyzed in seven days; Rabbit 2, paralyzed in seven days.

Harris' virus: Rabbit 1, discharged after thirty-eight days; Rabbit 2, paralyzed in seventeen days.

Pasteur virus: Rabbit 1, discharged after thirty-eight days; Rabbit 2, paralyzed in ten days.

1 to 4,000

Control: Rabbit 1, paralyzed in seven days; Rabbit 2, paralyzed in seven days.

Harris' virus: Rabbit 1, discharged in thirty-eight days; Rabbit 2, paralyzed in seven days.

Pasteur virus: Rabbit 1, paralyzed after six days; Rabbit 2, paralyzed in seven days.

The conclusions reached by Poor, Jelnick and Gibson is that the desiccated virus produces immunity more quickly than the Pasteur cords.

I have used this material during the past four years in the treatment of patients, and have been able to collect data on 1,159 patients treated with it. Of these cases, 359 were treated by me, 222 in the State Board of Health laboratory of Indiana by Dr. William Shimer, and 618 in the Charity Hospital, New Orleans, by Dr. M. Couret. Of this number, one died during the treatment, and one fourteen days after the first injection. With these two exceptions, there were no deaths and no cases of paralysis. If we follow the example of Pasteur and exclude these two cases the mortality is zero. But excluding one death in which symptoms developed on the tenth day during the treatment, and including the other, in which treatment had been completed, but in which symptoms developed on the fourteenth day after the first injection, there is a mortality of less than 0.1 per cent., a result that compares favorably with any of the other modifications.

Table 1 includes 319 patients treated by me in St. Louis and 618 by Dr. M. Couret in New Orleans.

TABLE 1.—DATA OF NINE HUNDRED AND THIRTY-SEVEN PATIENTS TREATED FOR RABIES

	Head	Hand and Forearm	Body and Lower Extremity	Contact	Total
Rabid	40	209	124	98	471
Probably rabid	25	159	95	..	279
Unknown	7	61	67	1	136
Probably not rabid	6	28	17	..	51
Total	..	...	...	..	937

Table 2 includes 222 patients treated by Dr. William Shimer, director of the Indiana State Board of Health laboratory, with virus furnished by Eli Lilly & Co.

TABLE 2.—DATA OF PATIENTS TREATED BY DR. SHIMER

Sex	No. Patients
Male patients	67
Female patients	32
Children, both male and female	123
Total	222

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Where Bitten or Exposed	No. Patients
Head	2
Face	26
Hands	67
Feet	13
Legs	36
Arm	25
Body	5
External genitals	1
Cut by knife	1
Abrasion on hands	45
Handling child dying of hydrophobia	1
	222

TABLE 3.—RESULT OF EXAMINATION OF ANIMALS

Exposure	No. Patients
Bitten by rabid dogs	99
Bitten by dogs with positive gasserian ganglion	60
Bitten by dogs, probably rabid	28
Bitten by dogs which got away	25
Bitten by dogs, probably not rabid	1
Cut by knife	1
Bitten or exposed to infection from saliva from cows whose brains were found to contain Negri bodies	8
	222

TABLE 4.—TREATMENT

	No. Patients
Seven injections, 6,750 units	62
Fourteen injections, 19,250 units	71
Eighteen injections, 27,350 units	99
	222

TABLE 5.—NATURE OF THE WOUNDS AND EXPOSURE

Character of Exposure	No. Patients
Slight bites	74
Severe bites	103
Exposed to infection by contact	44
Handling hydrophobia patients	1
	222

The amount of desiccated virus and the number of injections used in the experimental work and in the cases treated was decided on after a study of the scheme of Högyes. In this scheme Högyes injected 54.575 mg. of cord in fourteen days in light cases, and 94.47 mg. in twenty days in bites on the face and head. Most writers agree that immunity is produced by the more or less altered rabies organism, and that the degree of immunity is proportional to the number of infective specific organisms injected. The infectivity of the cord is such that 1/40 mg. is the least amount that will constantly infect rabbits.[7] Expressed in terms of infectivity, Högyes injected in mild cases 2,183 times the minimal infective dose; in severe cases,

3,898. Harvey and McKendrick calculate that in the Pasteur light scheme this number of times the minimal infective dose is 2,160.

The minimal infective dose of desiccated brain and cord is 1/250 mg., and one can easily inject many times the total infective doses usually contained in Pasteur's scheme with a much smaller proportion of foreign nerve material. I prefer to give 500 minimal infective doses, or units, at the first injection; 1,000 units at the second; 2,500 each at the fifth, sixth and seventh. In severe cases the daily dose after the fourth injection may be 3,000. The usual mild case is treated in six or seven days; severely bitten patients are treated ten to fifteen days. Mildly injured persons received from 7,000 to 10,000 units. Dangerously bitten patients have received 30,000 to 70,000 units, or twenty times more than that given by Pasteur. In the treatment of a dangerously bitten patient the following record will serve as an example:

J. M., man, aged 24 years, bitten July 8, 1915, on the septum of the nose by his own dog. The wound bled freely, but was not cauterized. The dog developed rabies two days later, and died five days later. Negri bodies were present. Treatment was begun six days after the injury. Injections were made as shown in Table 6.

TABLE 6.—ILLUSTRATIVE ANTIRABIC TREATMENT

Date	Amt., Mg.	No. Units
7/14	50	500
7/15, a. m.	15	1,000
7/15, p. m.	25	2,000
7/16, a. m.	10	2,000
7/16, p. m.	15	3,000
7/17, a. m.	15	3,000
7/17, p. m.	15	3,000
7/18	20	4,000
7/19, a. m.	15	3,000
7/19, p. m.	15	3,000
7/20, a. m.	15	3,000
7/20, p. m.	20	3,000
7/21	20	4,000
7/22	15	3,000
7/23	20	4,000
7/24	20	4,000
7/25	20	4,000
7/26	25	5,000
7/27	20	4,000
7/28	20	4,000
7/29	20	4,000
Total	315	66,000

Of the 1,159 persons treated with this material, two died of hydrophobia. Couret[9] states the single failure in the Charity Hospital cases was that of a 2-year-old negro child who received a slight wound over the right eye Oct. 6, 1915. Eight days later the mother applied for treatment, and the treatment was begun on that day. On the eleventh day of a fifteen-day treatment, the child developed symptoms of hydrophobia, and the treatment was discontinued. The child died two days later. The wound was not cauterized at the time the injury was inflicted, and when the patient came for treatment, the wound was completely healed.

The other death occurred in my own series. The history in this case is as follows:

L. P., man, aged 52, farmer, was bitten July 1, 1913, by his own dog, which was killed and in whose brain Negri bodies were abundant. The patient was thrown to the ground by the dog, which then grabbed the hand in his mouth with the resulting extensive lacerations and deep penetrating wounds. Treatment was begun five days later. The injections being as shown in Table 7.

TABLE 7.—TREATMENT IN THE CASE OF L. P.

Date	Mg.	No. Units
7/ 6/13, a. m.	40	500
7/ 6/13, p. m.	20	1,500
7/ 7/13, a. m.	..	1,000
7/ 7/13, p. m.	..	1,500
7/ 8/13, a. m.	..	2,000
7/ 8/13, p. m.	..	2,000
7/ 9/13, a. m.	..	2,500
7/ 9/13, p. m.	..	2,500
7/10/13	..	2,500
7/11/13	..	2,500
7/12/13, a. m.	..	2,500
7/12/13, p. m.	..	3,000
Total	60	24,000

The twelve injections were given within a period of seven days at the urgent request of the patient, who desired to return home at harvest time. After his return he worked in the sun during exceedingly hot weather and became very much exhausted. On July 21, twenty days after he was bitten and fifteen days after the first injection, symptoms of hydrophobia appeared. He died of convulsions on the twenty-seventh.

9. Couret: Personal communication to the author.

If the value of this material in antirabic treatment can be judged by this record of 1,159 cases treated with but these two failures, in both of whom the disease developed before the possibility of antibody formation, the results obtainable will compare favorably with those obtained by other modifications of the original method.

Assuming from these data that the material has an efficient immunizing power, we can see that it possesses another, though minor, advantage over the Pasteur method. The average time required for the complete administration of the treatment is less than one-half the time required by the Pasteur method. The 936 patients treated by Couret and by me averaged less than ten days per patient, a saving of more than 9,000 days of treatment over what would have been required had we followed the Pasteur scheme. This is a matter of great importance to those who are obliged to travel from home to the city for treatment. As a concrete instance, the State Board of Health of Indiana has a fund for caring for indigent patients while they are receiving antirabic treatment. In one year this amount spent by the state for board was $900 less than it would have been had these patients received the usual Pasteur scheme.

704 Metropolitan Building.

ABSTRACT OF DISCUSSION

DR. SAMUEL JAMES MELTZER, New York: I would like to ask Dr. Harris whether the dried virus could be pulverized and whether it could then stand the sterilization by dry heat without the effective part of the virus being destroyed. That the tissue, when dried, is more effective, reminds me of the statement of Dr. Novy that the addition of water to some substance reduces its anaphylactic effects.

DR. W. W. TOMPKINS, Charleston, W. Va.: I wish to report a case in which there was a short period of incubation. One year ago last August a patient was bitten on the hand by a dog. The wound was sucked and over the wound was placed ordinary tobacco. The following Saturday the patient

developed rabies with violent strangulation and choking and could not swallow fluids. On Saturday, one week later, I was called to travel a distance of seven miles, and found the patient with distressed and drawn features. He was rational, but afraid. I asked him to drive to town, and he said he would. The symptoms had already developed. At 2 or 3 o'clock that night he got out of the hospital and went back home. At 5 o'clock he had a severe convulsion and died. In this case I was impressed by the fact that in crossing the creek he had no difficulty about his larynx, but only when fluids were present. Three boys had been bitten by the same dog; the dog was killed and the head and spinal column sent to a pathologist, who said it was a case of genuine rabies. He advised that no time be lost, but that the cases be treated at once. One case was treated with serum, another by a "mad stone," the third by application of nitric acid to the wound. The question arises, was it a case of rabies or a mistaken diagnosis? A variety of treatments were tried and with equal good results.

Dr. Robert Alway Peers, Colfax, Calif.: We have had considerable experience with rabies during the past few years in California where rabies was epidemic and spread from the southern to the northern part of the state. Several hundred cases were treated at the State Laboratory at Berkeley. The length of time necessary to immunize a patient is extremely important, and any method which shortens the time of immunization is an advance. Not infrequently a person is bitten by a dog while an epidemic of rabies is prevalent in the community. It is not advisable to kill the dog at once because of the danger of killing the animal before the disease is advanced sufficiently to make a laboratory diagnosis possible. The dog should be kept chained and if he has rabies he will die within a few days. If the dog is kept several days before a diagnosis of rabies is made, there are then required twenty-one days treatment by the Pasteur method, and later fifteen days for immunization to become complete—more than forty days altogether, which is very near the danger line. For this reason, the method the doctor described, by shortening the time of immunization, is a great help.

UREMIA

A DIFFERENTIATION OF TYPES

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NEW YORK

When Bright noted an increase of urea in the blood and fluids of patients with severe nephritis and gave the name uremia to a group of symptoms likely to develop with these cases, he believed urea to be a highly toxic substance. The name uremia remains to us, although the term embraces now considerably more than urea intoxication. Under it are grouped several syndromes referable chiefly to the nervous system and with which no constant lesions are noted at necropsy outside the kidneys. Bright's observation that urea is increased in amount in the body fluids with certain renal defects established a principle which has been remarkably stimulating to later studies. This idea initiated that conception of uremia commonly called the retention theory, by which one means that some or all of the nitrogenous bodies normally excreted through the kidneys are, when these organs become diseased, retained in the body and give rise to symptoms. The corollary to this proposition, that the urine is specifically toxic, was debated and abandoned in the last century without elucidating any undisputed scientific facts.

So then we are still confronted by the question: Is the syndrome uremia due to a retention in the body of normal urinary substances, or is it induced by a wholly abnormal type of metabolism, resulting in new toxins? I am not intending to labor this question unduly, but I wish to bring to your attention some well-known facts which show just what may be expected from the retention of urinary bodies and then to apply these facts to uremia.

The state of complete anuria, that is, absolute retention, bears directly on this point. Whether induced by impacted renal calculus or by the removal of the only kidney or by such poisons as mercuric chlorid, the symptoms resultant are in all cases almost identical.

I have had an opportunity to study three persons in whom the only functioning kidney was removed surgically because of some diseased condition; the remaining kidney in these cases was infantile, atropic and of no use. These cases all presented a condition of anuria, hence of complete retention in the body of all substances normally excreted through the kidney. It is well known that with such cases there are few or none of those symptoms which demark our conception of spontaneous uremia. Convulsive seizures, for example, are not observed. Nervous phenomena are conspicuously wanting, gastro-intestinal disturbances absent or appear only as moribund manifestations. The last case I saw was without significant symptoms for eight days and then an increasing sopor developed and death ensued within a few hours. This is the common experience and Ascoli was positive that the picture is quite different from that associated with renal disease and he called this syndrome urinary poisoning. The same symptoms are found with anuria due to mercuric chlorid poisoning, of which we see so many cases in New York; and I have induced an analogous state in dogs by nephrectomy, by ligation of both ureters, and by ligation of the renal arteries. The essential positive symptoms, either with man or in experimental animals, resulting from absolute retention, are progressive asthenia and anorexia; later, stupor and death. These facts I bring out with some prominence, since they enter into the more complex picture of true uremia. Urinary poisoning is a pure type.

Urinary poisoning, as I have described it, is produced by some rather sudden change in the excretory organs resulting in a prompt flooding of the tissues

with nitrogenous waste products. Death is then a matter of days only. Now when the failure of elimination is not so rapid and the waste products accumulate in the tissue fluids more gradually, it is conceivable that the cells acquire a certain degree of tolerance and are not so injured as appears to be the case when the change is sudden. This conception has ample basis in analogy and explains prolongation of life under conditions which if effected suddenly lead quickly to dissolution. It is necessary to bear this possibility in mind as we proceed.

A rather close resemblance to the clinical picture of urinary poisoning is produced when, with advanced chronic nephritis of the hypertensive variety, there is added the complicating factor of cardiac dilatation and insufficiency. Let me explain just what appears to happen. With this type of nephritis the kidney has lost the power to secrete a concentrated urine and this is most conspicuous with respect to nitrogen. While a normal kidney on demand secretes urine containing 1.5 per cent. of nitrogen, the granular kidney may at best attain only 0.6 or 0.7 per cent., and not infrequently cannot arrive at 0.5 per cent. of nitrogen. Success then in freeing the body of its nitrogen waste is attained by increase of the urine volume. The normal kidney in secreting 1,000 c.c. of urine containing 1.5 per cent. nitrogen, has secreted 15 gm. of nitrogen, but the diseased kidney in order to secrete 15 gm. of nitrogen must secrete 2,500 c.c. of urine containing 0.6 per cent. nitrogen.

But with the increased urine volume the burden of work is transferred from kidney to heart. Now if the heart breaks down under its burden the volume of urine of course falls, and the nitrogen excretion falls with it, since the kidneys cannot accommodate themselves by concentration of urine as in pure cardiac disease. These conditions lead to nitrogen retention and an accumulation of slag in fluids and tissues. You will note that these conditions are the same in kind as

with urinary poisoning; the difference is in degree, and therefore the clinical picture is slower in developing and more protracted. There is here gradually developing stupor, asthenia and anorexia. There is added one important symptom, namely, a mild delirium, which may be simply a mental clouding associated with disorientation, chiefly of place; occasionally there are real delusions of the persecution type. Edema may or may not be marked, dependent apparently on the degree of cardiac embarrassment, since when a patient improves the edema is prone to diminish as the blood pressure becomes more elevated. Symptoms indicating irritation in the motor centers are not observed when this type is pure.

This type of uremia is a mixed picture, but fundamentally it is a urinary poisoning, a retention syndrome induced directly by cardiac failure. There is found, of course, in the blood an increase in nonprotein nitrogen, which may be considerable, occasionally but slight, in degree. This type of uremia has in my experience been a rather common sequel to protracted hypertension; existing in the beginning without marked evidence of renal damage, what we commonly regard as primary arteriosclerosis. When these cases escape their chief danger, cerebral hemorrhage, a nephritis usually develops, but the kidney found at necropsy, while showing fibrosis, does not present the degree of destruction of renal elements noted in some other types of nephritis.

The clinical picture of nephritis which we associate with the large white kidney appears to be as little complex in reference to physiologic function as any type of renal disease. The clinical manifestations are related chiefly to disturbances in water and salt excretion. There is no unanimity of opinion as to the interpretation to be given the facts, but all concur that the conspicuous departure from normal relates to poor excretion of water and salt, the consequent anasarca, and the relatively normal excretion of urea and other

nitrogen fractions. This type of nephritis but seldom progresses to uremia, it being the rule in my experience that protracted cases develop some terminal infection. Exceptionally, however, during the last period of life some uremic symptoms are in evidence. These are vomiting, headache, stupor, amaurosis due to edema of the retina, and finally coma.

Contrary to the statement of some, I have never seen convulsive seizures. The blood pressure remains normal, or subnormal. The blood and tissue analyses do not indicate any notable degree of nitrogen retention, even when corrected for the water excess. At necropsy, aside from nephritis, the conspicuous condition is edema, and this is peculiarly notable in the brain and meninges. Arguing from analogy, that is, the similarity of this picture clinically with some others associated with marked cerebral edema, I have felt that this edema must be in some way accountable for the cerebral symptoms. In our present state of ignorance concerning the causation of edema generally this idea cannot rest on a firm scientific basis. I have but one supporting fact, namely, that when lumbar puncture is done in these cases, the cerebrospinal fluid is found to be under increased pressure and after some fluid is removed there is a temporary clearing of the mental state of the patient. This hypothesis as to the causation of the stupor and coma observed in cases of nephritis with chlorid retention is advanced with every reservation. Until we understand edema we will not understand this type of uremia. The type is, I think, clear cut and associated with a form of nephritis which is well demarked by the functional change in respect to water and salt excretion,[1] the chloremique of Widal. Pathologically the kidney shows parenchymatous nephritis, that is, the large white kidney.

1. While the nitrogen metabolism shows no conspicuous abnormality, yet in every case that I have had an opportunity to observe a careful metabolic study has revealed a slight degree of nitrogen retention, a plus balance.

When this type of uremia is unmixed, there is never convulsive uremia as a sequel. On the other hand, a mixed nephritis may give rise to edema as a conspicuous symptom; but there is associated then also an increased blood pressure and an increased nonprotein nitrogen. When uncomplicated, the chlor-retention nephritis shows a normal or subnormal blood pressure and low nonprotein nitrogen. The degree of albuminuria helps not at all in the diagnosis.

Of the various manifestations due to uremia, none demarks a type so clearly as convulsive seizures. Convulsive or epileptiform uremia has been regarded by all students as different in causation, peculiar and specific. In discussions of uremia with convulsions it is commonly classified as a toxemia, although a toxin has never been isolated. There are several facts that I wish to call to your attention which lend some support to the idea that a toxin may be present. In the first place these cases, on metabolic study, all show periods of clear-cut nitrogen retention. There is as a rule an increase of nonprotein nitrogen in the blood also. Now, whereas the urine shows but 6 or 7 per cent. undetermined nitrogen, the blood nitrogen may be 20 per cent. or even more undetermined. This fact indicates either a selective excretion or formation of non-excretable substances. These facts apply more or less to all types of nephritis with retention. Finally, all the organic poisons known are nitrogen containing compounds. Considerations of this sort brought out in my studies several years ago led me to think that an effort might be made to isolate a specific toxin from the blood or tissues in these cases and I believe this has been accomplished. A crystalline substance has now been separated from the blood in a series of cases of convulsive uremia. This substance is highly toxic; 200 c.c. of blood contains enough to kill a guinea-pig. The substance cannot be detected in normal blood or in blood in any diseased state except uremia of this type. The symptoms produced in animals after injec-

tion into the peritoneal cavity are dyspnea, fecal discharges, convulsions or muscular twitchings, coma and death. Of the chemical nature of this compound, its source in the body, its effect in producing organic changes, we cannot speak at this time.

Granting for the moment that this substance is specific and peculiar for one type of uremia, then the question arises, is it a normal catabolic substance which is in health excreted in urine, or is it a product of abnormal metabolism, a result of perverted processes instituted by renal disease? If this compound is a normal excretory product, then it should accumulate in blood and tissue in conditions of anuria; but as already mentioned, these cases do not resemble uremia. One case of complete anuria due to the removal of the sole functioning kidney (the other being infantile and atrophic) was investigated. This patient died nine days after the operation and immediately post mortem about 1 liter of blood was aspirated from the jugular vein. This blood yielded no toxic substance. The degree of retention is indicated by the nonprotein nitrogen which was 126 mg. per 100 c.c. of blood. The evidence of one case is not adequate, but it supports the original conception that in the convulsive type of uremia there is an abnormal metabolism, as well as a nitrogen retention.

There are then, according to my present conception, three pure basic types of uremia. The first is a simple retention of urinary nitrogenous waste, a urinary poisoning; the second is due to defective water and salt metabolism, resulting in cerebral edema; the third type is a toxemia, resulting from an abnormal catabolism. Two of these are dependent wholly on failure of excretion, either of nitrogen, water, or salt; a third, while it may show each and all of the three enumerated defects, is demarked by another element foreign to normal catabolism and resulting in toxin formation, which is manifested clinically by convulsive seizures.

Now clinically we see only exceptionally these types uncomplicated; just as we see but exceptionally pure types of renal disease; and this is so whether we consider the case from the functional physiologic aspect or that of microscopic pathology. The majority of cases that evidence nitrogen retention also have more or less edema, at least at periods. Those in which edema is the striking phenomenon have usually slight or marked nitrogen retention if the case is studied for sufficient periods. The sections from these kidneys do not disclose a uniform picture; in one field the tubules or some part of these tubules appear chiefly diseased, in another section from the same kidney it may be that glomeruli seem more damaged, or the arterioles. And it is impossible to surmise from the appearance of a damaged tubule as to its degree of functional impairment. Hence uremia is ordinarily a complex picture, resulting from a mixture of physiologic defects and stamped clinically by that one which is predominant. Only by a rather careful study of many cases at bedside, in the laboratory, and at the autopsy table does one arrive at a conception of pure types. Pure types do occur, but they are the exception in my experience. These types fall into three main groups, depending on the nature of the functional defect in the kidney: (1) retention type, the urinary poisoning of Ascoli; (2) cerebral edema type; (3) toxic type, or epileptiform uremia.

THE VALUE OF RECENT LABORATORY TESTS IN THE DIAGNOSIS AND TREATMENT OF NEPHRITIS

WITH SPECIAL REFERENCE TO THE CHEMICAL EXAMINATION OF THE BLOOD *

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Chemical researches have recently added much to our knowledge of many pathologic conditions, but it is doubtful if any disorder has profited more than nephritis. The investigations have given us a clearer insight into this condition, have aided in diagnosis and prognosis and finally have been a guide to treatment.

For a long time the clinician has been accustomed to rely on the examination of the urine for his index of the efficiency of the kidney. In nephritis the volume, specific gravity, albumin, casts, and occasionally, the chlorids and total nitrogen or urea have covered the examinations made. More recently the ability of the kidney to eliminate various substances administered, either per os or parenterally, has been practically employed as a means of determining its functional activity. The phenolsulphonephthalein test of Rowntree and Geraghty [1] and the lactose and potassium iodid tests of Schlayer [2] have found extensive

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1. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1910, i, 579.

2. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910-1911, ci, 333.

use, especially the former. The phenolsulphonephthalein test, although introduced only six years ago, has received almost universal recognition.

The finding of albumin and casts in the urine is unquestionably of great diagnostic value in nephritis and of considerable prognostic value in the acute and subacute forms of the disease. In the chronic forms, however, there has been a growing tendency to place less and less reliance on this information from the standpoint of prognosis.

Recently Mosenthal [3] has excellently discussed a number of well-known clinical observations on the urine. He has pointed out that a very considerable amount of information may be obtained from the observations of the volume, specific gravity, chlorids and nitrogen output of the night and two-hour day urine specimens of nephritic patients, when placed on a definite test diet. The normal individual is able to secrete at night a urine of high concentration, but in nephritis the specific gravity may be fixed at a constant level with a very definite concentration of chlorids and urea. The importance and diagnostic value of this has not been fully appreciated, primarily because of the time and care required in the collection and analysis of the specimens.

The introduction of the phenolsulphonephthalein functional kidney test by Rowntree and Geraghty in 1910 not only supplied us with a most valuable diagnostic and prognostic test, but furnished the impetus in this country to numerous investigations on the functional activity of the kidney. With the introduction three years later of simple methods of blood analysis, especially at the hands of Folin and his co-workers, the possibilities of these new methods as practical diagnostic tests were quickly appreciated.

In some quarters the nonprotein or incoagulable nitrogen alone has been employed as a test of kidney activity, while in others the urea has been utilized.

3. Mosenthal: Arch. Int. Med., 1915, xvi, 733.

McLean,[4] in particular, has emphasized the value of a comparison of the urea of both blood and urine, somewhat after the method employed by Ambard. So far as we are aware, in institutions other than our own, the uric acid has been used chiefly in connection with the diagnosis of gout.

Although considerable attention has been given to the urea and nonprotein nitrogen [5] of the blood in nephritis, scant consideration has been accorded the uric acid and creatinin. It is true that the greater part of the waste nitrogen is eliminated in the form of urea, but it does not necessarily follow from this that data on uric acid and creatinin are unimportant and uninteresting. We do not believe that it is possible to make satisfactory deductions regarding nitrogen retention from the urea or nonprotein nitrogen determinations alone. The scheme we now employ for the examination of the blood entails the determination of the uric acid, urea, creatinin and sugar as a routine with estimations of the carbon dioxid combining power according to Van Slyke in cases in which this appears to be indicated. The determination of the urea concentration of the blood is, we believe, of more value than that of the nonprotein nitrogen for the reason that it represents the retention of a definite compound and, further, is more easily and accurately determined.

The phenolsulphonephthalein test is so far superior to any other general functional kidney test that one scarcely need mention any other test in a brief discussion. In comparison with the chemical examination of the blood it is believed that the latter method gives much more definite information in many cases. In our work, however, we have almost invariably employed the phenolsulphonephthalein test, either previous to or in conjunction with the blood examination. Another

4. McLean: Jour. Exper. Med., 1915, xxii, 212, 366; Clinical Determination of Renal Function by an Index of Urea Excretion, THE JOURNAL A. M. A., Feb. 3, 1916, p. 415.

5. A very complete discussion has been given by Tileston and Comfort: Arch. Int. Med., 1914, xiv, 620.

very important point in favor of the chemical examination of the blood, compared with the quantitative examination of the urine, is the difficulty and time required in the collection of urine specimens. It is our opinion that the chemical examination of the blood, when good laboratory facilities are available, requires less of the physician's time and gives him more definite information.

Both Mosenthal [6] and Foster [7] have called attention to the fact that the increase in the nonprotein nitrogen of the blood in nephritis is quite insufficient to account for the amount of nitrogen retention. Despite this fact, the degree of the retention of the various waste products affords an excellent index of the severity of the condition, and probably a fair index of the retention in the later stages of the disease, particularly as regards the uric acid and creatinin.

In our studies [8] on the uric acid, urea and creatinin of the blood it was soon noted that high uric acids were frequently found wthout any other retention, while creatinin appeared to be retained only in the last stages of the disease. In comparing the concentration of these waste products in blood and urine, it was observed that the kidney was able to concentrate the creatinin 100 times, the urea eighty times, but the uric acid only about twenty times. In other words, it would appear that, normally, creatinin is the most readily and uric acid the least readily eliminated by the kidney, with urea standing in an intermediate position. From this it is logical to expect that the excretion of uric acid would be the first to be impaired, and in nephritis our blood studies appear to indicate that a retention of uric acid is generally the first to become evident. In harmony with this hypothesis, we should next expect a

6. Mosenthal and Richards: Arch. Int. Med., 1916, xvii, 329.
7. Foster and Davis: Am. Jour. Med. Sc., 1916, cli, 49.
8. Myers and Fine: Jour. Biol. Chem., 1915, xx, 391. Myers and Lough: Arch. Int. Med., 1915, xvi, 536. Myers, Fine and Lough: Arch. Int. Med., 1916, xvii, 570. This paper describes the estimation of the uric acid, urea and creatinin in the blood. At the suggestions of one of us (M.), E. Leitz of New York has recently made a very simple and inexpensive colorimeter which may be used for these determinations.

retention of urea and lastly that of creatinin. That such is the case is quite evident from an examination of Table 1, giving analyses of typical cases of patients suffering from various stages of nephritis.

According to this view a retention of uric acid should constitute one of the early signs of incipient interstitial nephritis, while an appreciable retention of creatinin should indicate a grave impairment in the functional condition of the kidney and therefore should be a valuable prgonostic test.

Theoretically, the creatinin of the blood should be a safer index of a lowered kidney activity than the urea, for the reason that creatinin on a meat free diet is entirely endogenous in origin and its formation (and elimination, normally) very constant. For the same reason it must be evident that a lowered nitrogen intake may reduce the work of the kidney in eliminating the urea and to a certain extent the uric acid, but cannot affect the creatinin to any extent. The handicap of a high creatinin accumulation, the kidney is, apparently, never able to overcome.

Our blood studies show that many early cases of nephritis, probably of the interstitial type, give blood pictures in which the essential feature is the high uric acid. The urea and creatinin are frequently normal, though sometimes appreciably increased. As the condition of the cases of this type become more severe, the retention of urea increases, until we have high values for urea as well as uric acid. If improvement takes place, the concentration of urea gradually falls until the picture is that of the preceding group. If, on the other hand, the case goes on to fatal termination, the retention of uric acid and urea is followed by that of creatinin, the concentration of which may reach twenty times the normal.

As already noted, the rise in the concentration of the uric acid of the blood appears to be an excellent early sign of chronic (interstitial) nephritis.[9] The diagnos-

9. Myers, Fine and Lough: Footnote 8.

TABLE 1.—URIC ACID, UREA NITROGEN AND CREATININ OF BLOOD IN INTERSTITIAL NEPHRITIS *

Date, 1915-16	Case	Age	Sex	Diagnosis	Condition	Mg. per 100 C.c. of Blood			Phthalein 2 Hrs., per Cent.	Systolic Blood Pressure	Urine	
						Uric Acid	Urea N	Creatinin			Albumin	Casts
I												
9/17	H. L.	28	♂	Pulmonary tuberculosis	Unchanged	6.5	16	2.7	58	130	++	+
8/10	E. H.	41	♂	Pericarditis	Unchanged	5.6	13	2.1	45	150	—	—
10/12	F. D.	45	♂	Interstitial nephritis	Unchanged	5.5	12	2.5	37	185	—	+
3/ 6	B. D.	35	♀	Diffuse nephritis	Unchanged	9.6	19	2.4	45	175	+	+
II												
8/11	J. J.	65	♂	Early interstitial nephritis	Unchanged	9.5	25	2.5	13	185	+	+
7/21	D. S.	56	♂	Early interstitial nephritis	Unchanged	6.6	24	3.3	26	185	—	+
9/21	D. D.	52	♂	Early interstitial nephritis	Unchanged	8.7	20	3.6	20	100	+	+
8/ 3	C. M.	54	♂	Early interstitial nephritis	Unchanged	6.3	31	2.0	23	150	—	—
III												
1/ 6	L. P.	57	♂	Moderately severe chronic interstitial nephritis	Improved	8.0	80	4.8	0	240		
8/ 1						4.9	17	2.9	10	170	++	++
4/23	J. P.	34	♂	Moderately severe chronic diffuse nephritis	Improved	8.3	72	3.2	25	238		
5/21						5.3	21	1.9	43	145	+++	++
1/15	W. C.	49	♂	Moderately severe chronic diffuse nephritis	Improved	9.5	44	3.5	38	210		
1/28						2.5	19	1.9	52	120	++	++
IV												
4/11	E. C.	50	♀	Typical fatal case of chronic interstitial nephritis	Died	22.4	236	16.7	0	210	++	Pus
3/23	T. D.	34	♂	Typical fatal case of chronic interstitial nephritis	Died	15.0	240	20.5	2 - 3	225	++	+
1/25	S. H.	37	♂	Typical fatal case of chronic interstitial nephritis	Died	14.3	263	22.2	0	220	++	+
4/15	J. W.	34	♂	Typical fatal case of chronic interstitial nephritis	Died	8.7	144	11.0	Trace	225	+	+

* Normal findings: uric acid from 2 to 3 mg.; urea nitrogen, from 12 to 15 mg.; creatinin, from 1 to 2.5 mg. per 100 c.c.
♂ signifies male; ♀ signifies female.

tic value of the blood uric acid in comparison with other tests is well brought out in Table 2. It is obviously important in this connection to bear in mind the association of uric acid retention with gout,[10] although the retention here must likewise be ascribed to the same cause, namely, a lowered kidney permeability.

As a prognostic test the blood creatinin has been found of very great value. It is superior to the phenolsulphonephthalein test, since changes in the patient's condition are clearly shown, while the phenolsulphonephthalein test is continuously negative. Attention was called to this test nearly a year ago,[11] but we now have more than three times as many cases on which to report. All patients whom we have been able to follow for any length of time who had over 5 mg. creatinin to 100 c.c. of blood have died. Our observation on these cases, together with the phenolsulphonephthalein outputs, are summarized in Table 3. In this list it will be noted that only three (one patient has since died) of the patients having over 5 mg. remain alive, and these are patients who have been allowed to leave the hospital only recently. Only one of these patients, however, can be called improved.

Our experience with the ratio between the urea of the blood and urine according to the formula worked out by Ambard and by McLean has been rather disappointing. In comparing the uric acid, urea and creatinin of the blood and the phenolsulphonephthalein of the urine with the index of McLean[4] in thirty cases, the index appeared to give no additional information over the blood urea with the possible exception of one case. In this case a blood urea nitrogen of 33 mg. was encountered with an index of 198. In the above thirty cases the indexes ranged from 3 to 342. It is quite possible that this is too small a number of

10. Fine: The Relation of Gout to Nephritis, as Shown by the Uric Acid of the Blood, THE JOURNAL A. M. A., June 24, 1916, p. 2051.
11. Myers and Lough: Footnote 8.

TABLE 2.—THE URIC ACID OF THE BLOOD IN CASES OF INCIPIENT INTERSTITIAL NEPHRITIS

Case	Age	Sex	Diagnosis, Remarks	Mg. to 100 C.c. of Blood			Phthalein, 2 Hrs. Output, per Cent.	Blood Pressure		Urine	
				Uric Acid	Urea Nitrogen	Creatinin		Systolic	Diastolic	Albumin	Casts
1. J. J.	65	♂	Interstitial nephritis	9.5	25	2.5	18	185	90	+	+
2. E. B.	46	♀	Fibrillation	9.3	14	2.9	44	120	90	—	—
3. D. D.	52	♂	Cirrhosis of liver, interstitial nephritis, chronic alcoholism	8.7	20	3.6	20	100	87	+	+
4. B. D.	25	♀	General edema	7.7	20	2.6	45	168	100	+	--
5. M. K.	49	♂	Carcinoma of stomach	7.5	16	2.2	50	150	90	—	+
6. D. S.	56	♂	Interstitial nephritis	7.1	16	2.0	26	185	110	—	+
7. A. R.	57	♂	Carcinoma of stomach, interstitial nephritis	6.8	20	1.8	40	140	80	—	+
8. H. L.	23	♂	Pulmonary tuberculosis, tuberculosis of kidney	6.5	16	2.7	58	130	90	++	+
9. C. M.	54	♂	Hypothyroidism, interstitial nephritis	6.3	31	2.0	45	150	90	—	—
10. M. McA.	44	♂	Syphilis, interstitial nephritis	6.3	17	2.7	38	185	80	++	+
11. W. B.	71	♂	Chronic arthritis, arteriosclerosis, interstitial nephritis	6.1	12	2.4	65	145	80	+	+
12. E. H.	41	♂	Pericarditis, moderate alcoholism	5.6	13	2.1	45	150	65	—	—

cases from which to make deductions, although Addis and Watanbe[12] recently concluded that "The rate of urea excretion in man varies under physiologic conditions in a manner which cannot be explained by the concentrations of urea in the blood and urine." Dr. Watanabe has been kind enough to recalculate some of their data into terms of the McLean index, the results indicating that according to this formula the indexes on normal subjects may vary between 25 and 250, a rather wide variation.

The patients whom we have had an opportunity of studying have been largely patients suffering from chronic interstitial (or true) nephritis. The condition of the blood in parenchymaous nephritis (nephrosis) is in our experience very different from that of the interstitial type. In the parenchymatous form one finds only a moderately increased blood urea, but differing from the interstitial type; an increased concentration of chlorids is frequently present, as might be expected from an accompanying edema.

As is evident from dyspnea, many advanced cases of nephritis develop an acidosis, due not to an increased formation of acid substances as in diabetes, but to the impaired elimination of the normally formed acid substances. During the last two or three years we have been accustomed to ascertain the degree of this acidosis from the carbon dioxid tension of the alveolar air[13] or the hydrogen ion concentration of the blood. Van Slyke[14] has recently shown that the degree of this acidosis may be more simply and more accurately determined by ascertaining the carbon dioxid combining power of the blood plasma. For this purpose he has ingeniously devised a very simple apparatus. This instrument has been in continuous

12. Addis and Watanabe: Jour. Biol. Chem., 1916, xxiv, 203.

13. Very recently Marriott (The Determination of Alveolar Carbon Dioxid Tension by a Simple Method, THE JOURNAL A. M. A., May 20, 1916, p. 1594) has described a simple technic for carrying out this test, thus rendering it directly available to the clinician.

14. Van Slyke, Stillman and Cullen: Proc. Soc. Exper. Biol. and Med., 1915, xiii, 39.

TABLE 8.—THE PROGNOSTIC VALUE OF THE CREATININ OF THE BLOOD IN NEPHRITIS

	Case	Blood Creatinin, Mg. to 100 C.c.	Phthalein, 2 Hr. Output, per Cent.	Termination		Case	Blood Creatinin, Mg. to 100 C.c.	Phthalein, 2 Hr. Output, per Cent.	Termination
1.	W. F.	33.3	...	Died	18.	J. W.	11.0	3 to 1	Died
2.	E. M.	28.6	0	Died	19.	J. D.	10.7	0-5-4-3-6	Died
3.	S. H.	22.2	0	Died	20.	C. G.	10.0	0	Died
4.	T. D.	20.5	2 to 3	Died	21.	S. W.	9.1	0	Died
5.	I. D.	20.0	0	Died	22.	V. A.	8.3	6-4-2	Died
6.	P. J.	20.0	0	Died	23.	J. S.	7.4	.....	Died
7.	E. L.	18.9	0	Died	24.	W. G.	7.0	.....	Died
8.	M. M.	17.8	...	Died	25.	E. W.	6.7	5	Died
9.	E. C.	16.7	0	Died	26.	A. F.	6.1	9	Died
10.	W. O'C.	16.6	Trace	Died	27.	M. R.	5.9	3	Died
11.	M. K.	14.7	.....	Died	28.	J. McC.	5.6	2-7-10	Improved
12.	K. K.	14.7	0	Died	29.	V. R.	5.5	.....	Died
13.	J. H.	14.3	.....	Died	30.	M. N.	5.4	13-4	Stationary*
14.	E. P.	12.7	0 to 1	Died	31.	E. E.	5.3	10	Died
15.	W. W.	12.5	0	Stationary	32.	A. D.	5.2	.....	Died
16.	M. O.	11.1	0	Died	33.	T. K.	4.9	.....	Died
17.	K.	11.1	0 to 3	Died	34.	L. P.	4.8	0-10-31	Improved

* This patient has since died with a creatinin of 12.5 at time of death.

use in our laboratory for the past year. Normally the carbon dioxid combining power varies from 53 to 77 c.c. (corrected) per 100 c.c. of plasma. In nephritis it is generally somewhat reduced, 40 to 50, but may fall to as low as 25 shortly preceding death.[15] It would appear that in some cases the acidosis was a more important factor in the terminal symptoms than the nitrogen retention. As a guide to the treatment of the acidosis the determination has been found very valuable. One case may be mentioned. W. C. (Table 1, Group 3, Case 3) was admitted in coma with a carbon dioxid of 22. After an infusion of sodium bicarbonate, the patient quickly revived and on the second day showed a carbon dioxid of 58.

That many advanced cases of diabetes develop nephritis is a well-known clinical observation. In the early cases of diabetes there is a direct relation between the hyperglycemia and glycosuria, but this is certainly not true in cases of long standing with nephritis. It has been recognized for some time that hyperglycemia was present in many cases of advanced interstitial nephritis, though glycosuria was absent. The blood picture that we have observed in some cases of advanced diabetes is typical of interstitial nephritis,[9] that is, high uric acid values, frequently with moderate retention of urea. These patients had marked hyperglycemias, in one case 1.1 per cent., but were unable to secrete urines of high sugar content. Cases might be cited[16] with blood sugars up to 0.3 per cent. and above without glycosuria. The condition the clinician is endeavoring to treat by restricting the carbohydrate of the diet is the hyperglycemia, but the glycosuria is sometimes a very poor index to this condition. Since the determination of blood sugar may now be very simply carried out, the estimation of the sugar of the urine should be supplemented by the determination of the sugar of the blood.

15. Quintard and Fine: Unpublished Observations.
16. Myers and Bailey: Jour. Biol. Chem., 1916, xxiv, 147. This paper describes the method of blood sugar estimation.

COMMENT

Of the large number of methods used in the past few years to estimate the functional capacity of the kidney, we feel that the following are of practical use to the general practitioner: the phenolsulphonephthalein test, the determination of the fixation of the specific gravity and of nocturnal polyuria (an elimination of over 400 c.c. between 6 p. m. and 6 a. m. being an indication of renal involvement), and the estimation of the blood content of uric acid, urea, creatinin, sugar and carbon dioxid combining power. These tests are distinct contributions to medicine and have come to stay.

The use of renal test meals gives us much valuable information, but because they necessitate the careful weighing of foodstuffs and the exact collection and analysis of specimens of urine, their use will be largely confined to institutions.

The modern dietetic treatment of nephritis is based on the ability of the body to metabolize food stuffs and to eliminate their end-products; also on the permeability of the kidney to salt, water and nitrogen. By means of the newer methods of urine and blood analysis, the effect of a given diet can at once be determined. It is obvious that in cases of salt, water or nitrogen retention the indications are to give either a salt-free limited fluid or low protein diet, as the case requires. In cases of nephritis with high nitrogen retention, an almost exclusively carbohydrate diet, sugar in lemonade, arrowroot and cornstarch puddings are given for a few days.

The amount of nitrogen retention in the blood serves as a most excellent guide in the giving of protein. The use of a salt-free diet in cases of parenchymatous nephritis with edema and salt retention gives prompt results.

CONCLUSIONS

An increase in the uric acid of the blood would appear to be of considerable value as an early diagnostic sign of incipient nephritis.

The urea of the blood has been found very valuable as a guide to the treatment of moderately severe cases of nephritis, since any change in the patient's condition is quickly perceptible.

As a prognostic test the blood creatinin has been found of very great service, over 5 mg. to 100 c.c. having invariably proved fatal after the lapse of a comparatively short period of time. During the terminal stages of the disease the concentration of the creatinin gradually rises, reaching 15 to 30 mg. in most cases at death.

The determination of the carbon dioxid combining power of the blood plasma according to the method of Van Slyke is a valuable index to the acidosis of nephritis, from the viewpoint of both diagnosis and treatment.

In cases of advanced diabetes complicated with nephritis, the glycosuria or absence of glycosuria is a very poor guide to the hyperglycemia, since the nephritis has lowered the permeability of the kidney for sugar. In these cases the estimation of the sugar of the urine should always be supplemented by the determination of the sugar of the blood.

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A COMPARATIVE STUDY OF TESTS FOR RENAL FUNCTION

PHENOLSULPHONEPHTHALEIN, NONPROTEIN NITROGEN AND UREA NITROGEN OF THE BLOOD, AMBARD'S COEFFICIENT OF UREA EXCRETION, AND THE TEST MEAL FOR RENAL FUNCTION *

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The term "renal function" is generally accepted to mean eliminative power of the kidneys. For clinical purposes, many workers in this field have regarded renal function as a unit, and the phrase "testing renal function as a whole" has become a by-word in medical phraseology. While such a conception of the kidney's acting as an entity, all of its component physiologic factors diminishing or increasing their efficiency synchronously, may have the advantage of simplicity, it does not accord with the known facts. It is a matter of routine observation that the diseased kidney may retain water, or salt, or urea, or phosphates, or sulphates, or any of the urinary constituents, and allow the remainder to pass freely. We know that the glomeruli and the various subdivisions of the uriniferous tubules are structures with widely varying physiologic functions and are affected to an unequal degree by different toxic substances. Extrarenal factors, such as secondary anemia, fever, cardiac failure, cystitis, prostatic disease, etc., are all mirrored in changes in the renal function which do not resemble one another in the least. Therefore, to speak of "test-

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ing renal function as a whole" is to set a false standard. Of the various tests for renal function, each has its own significance, and a greater insight will be obtained into the characteristics of kidney disease when physicians will no longer advocate one test blindly to the exclusion of all others, but will endeavor to interpret each one according to its significance. It is from this point of view that the following studies are presented.

INTERPRETATION OF THE INDIVIDUAL TESTS FOR RENAL FUNCTION

The phenolsulphonephthalein test is so widely used and its value so generally appreciated that it scarcely requires comment. Rowntree[1] and his collaborators have maintained that after intramuscular injection, a urinary excretion of the drug of 60 per cent. or more in two hours is normal and that "when the drug was continuously excreted in traces or not at all, a grave prognosis was to be given even without signs of uremia." Following these hints and the deductions from our own experience, the degree of impairment of renal function, as indicated by the various percentages excreted, have been set down in Table 1.

It is impossible to be dogmatic in regard to what constitutes the upper normal level of nonprotein nitrogen and urea nitrogen of the blood. Foster[2] found a maximum of 44 mg. of nonprotein nitrogen per hundred c.c. of blood in supposedly normal individuals. Tileston and Comfort[3] demonstrated 32 mg. after a meal in a heavy meat eater. Under ordinary circumstances, the maximum obtained by these authors was 25 mg., which agreed very closely with the results of Folin and Denis.[4] It would seem that, unless there be

1. Rowntree, L. G., and Fitz, R.: Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, Arch. Int. Med., March, 1913, p. 258.
2. Foster, N. B. Functional Tests of the Kidney in Uremia, Arch. Int. Med., October, 1913, p. 452.
3. Tileston, Wilder, and Comfort, C. W., Jr.: The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Method, Arch. Int. Med., November, 1914, p. 620.
4. Folin and Denis: Jour. Biol. Chem., 1913, xiv, 29.

a very high protein intake, 30 mg. of nonprotein nitrogen per hundred c.c. of blood is a reasonable upper normal limit. The usual hospital bill of fare certainly does not furnish such a diet. Any value above 30 mg. in the present series of cases has, therefore, been regarded as indicating some degree of renal insufficiency. It is generally acknowledged that a retention of over 90 mg. of nonprotein nitrogen per hundred c.c. of blood indicates a very great increase, and it has been so considered here (Table 1). The urea nitrogen has been plotted out on the scale of impairment of renal function with the nonprotein nitrogen as a guide, keeping in mind the fact that in normal individuals the urea nitrogen constitutes about 50 per cent. of the total nonprotein nitrogen, while, with retention of the nitrogenous waste products, the percentage has a distinct tendency to increase (Table 1).

The upper normal limits of urea nitrogen have also been the subject of frequent experimentation. Schwartz and McGill,[5] after reviewing the extensive literature on the subject, consider urea nitrogen values above 12 mg. per hundred c.c. (0.25 gm. urea per liter) as abnormal. Myers, Fine and Lough[6] recently expressed the belief that 15 mg. of urea nitrogen per 100 c.c. of blood was the upper normal limit. McLean[7] demonstrated urea nitrogen as high as 23 mg. per hundred c.c. (0.5 gm. urea per liter) in normal individuals, but adds that within the limits of 14 to 23 mg. urea nitrogen per hundred c.c. of blood (0.3 to 0.5 gm. per liter) "a blood urea figure may be quite normal, or may occur with retention." It would seem, therefore, that the consensus of opinion points to determinations yielding a urea nitrogen figure above 15 mg. in 100 c.c. of blood as revealing the possibility of nitrogen retention, which is at least worthy of closer

5. Schwartz, H., and McGill, C.: Blood Urea Determinations in Two Hundred and Eleven Cases, Arch. Int. Med., January, 1916, p. 42.

6. Myers, V. C.; Fine, M. S., and Lough, W. G.: Significance of Uric Acid, Urea and Creatinin of Blood in Nephritis, Arch. Int. Med., April, 1916, p. 570.

7. McLean: Jour. Exper. Med., 1915, xxii, 212.

TABLE 1.—SCALE OF DEGREE OF IMPAIRMENT OF RENAL FUNCTION AS INDICATED BY THE TESTS EMPLOYED

Degree of Impairment of Renal Function	Phenol-sulphone-phthalein, per Cent.	Nonprotein N of the Blood, Mg. per 100 C.c.	Urea N of the Blood, Mg. per 100 C.c.	Ambard's Coefficient of Urea Excretion	Test Meal for Renal Function					
					Night Urine		Variations in Sp. G. When the Highest Sp. G. is:			
					C.c.	Sp. G.	18	17-15	14 and 13	12—
Normal..... 0	60+	30—	15—	0.090—	400—	18+	9+			
Slight..... +	59-40	31-45	16-27	0.091-0.115	401-600	16 and 17	8-5	6+		
Moderate..... ++	39-25	46-65	28-44	0.116-0.220	601+	15—	4—	5 and 4	6+	
Marked..... +++	24-11	66-90	45-64	0.221-0.350	.....	.....	.....	3—	4 and 5	6+
Maximal.....++++	10- 0	91+	65+	0.351+	.....	.....	.....	.....	3—	5—

investigation. For the other tests discussed here, absolute values for the normal may be given. For the nonprotein nitrogen and the urea-nitrogen of the blood, however, this is impossible because of the great influence dietary habits have on the level of these substances in the blood.

Ambard's coefficient of urea excretion expresses numerically the relation which exists between the concentration of urea in the blood and the rate of excretion of urea in the urine. It is calculated from the formula:

$$K = \frac{Ur}{\sqrt{D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}}}$$

In which K = The coefficient of urea excretion.
Ur = Urea grams per liter of blood.
D = Urea grams excreted in urine in twenty-four hours.
C = Urea grams per liter of urine.
P = Body weight in kilograms.
70 = Standard body weight in kilograms.
25 = Standard concentration of urea grams per liter of urine.

The formula is derived from Ambard's laws of urea excretion, concerning whose details the reader is referred elsewhere.[8] The normal coefficient usually ranges from 0.06 to 0.09. When the values rise above 0.09, some impairment of the power of the kidney to excrete urea is indicated. Inability of the kidney to eliminate urea in proportion to the concentration of the blood urea results in an increase in Ambard's coefficient. In a normal individual it will remain within the limits mentioned, no matter what the height of blood urea; in cases with impaired renal function, however, the kidney does not answer the diuretic stimulus of the blood urea adequately, too little urea is put out, and the result is a rising coefficient, whether the urea in the blood be high or low. The degree of impairment of renal function, as indicated by the various levels of Ambard's coefficient, are indicated in Table 1.

8. Ambard: Physiologie normale et pathologique des reins, Paris, 1914. McLean, F.: Jour. Exper. Med., 1915, xxii, 212.

The test meal for renal function consists of the two hourly collection of urinary specimens during the day, while the patient is on a full diet, and of a ten to twelve hour specimen at night. No food or fluid is taken except at meal times. The collection of the night specimen is begun three hours after the evening meal. Under these circumstances, a normal test yields a maximum specific gravity of 1.018 or more, the specific gravity varies 9 points or more from the highest to the lowest, and the night urine is small in amount (400 c.c. or less) and of high specific gravity (1.018 or over). These criteria are the same as those originally demanded of a normal test, with the exception that a difference of 9 degrees between the highest and lowest observations has been called normal,[9] instead of 10. A lowering of the maximal specific gravity, a fixation of the specific gravity and a nocturnal polyuria are the signs indicating a diminished renal function. Table 1 gives the various degrees of impairment as indicated by the test meal for renal function, as compared to the other tests. The salt, nitrogen and other urinary constituents may be determined in these specimens, and valuable information may be obtained as to the ability of the body to excrete these substances. However, the simple procedure of measuring the volume of the urine and determining the specific gravity yields sufficient data to give an adequate idea of renal function in many respects, and the quantitative chemical determinations may be resorted to when more detailed information is desired.

In order to study the relation to one another of the evidences of impaired renal function obtained by these various tests, a somewhat arbitrary scale of four degrees of impairment — slight, moderate, marked and maximal — was determined on. The exact figures which the majority of experienced observers consider as indicating normal function, and these various

9. Mosenthal, H. O.: Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine, Arch. Int. Med., November, 1915, p. 733.

degrees of subnormal function, were selected, and are shown in Table 1. The findings in over 200 patients were grouped in accordance with this scale.

A comparative table of this nature has heretofore not been seriously advocated. It has very distinct advantages in that it makes the judgment of laboratory findings very precise. However, it has its drawbacks in that it would tend to make the physician more mechanical in the interpretation of the facts laid before him and lead him astray, if the figures were not judged in connection with other clinical data. It is our belief that a scale indicating impaired function, as this one does, is a distinct aid when used correctly. In the first place, it calls attention without fail to impaired function whenever it is present, and it brings before the observer a distinct conception of the degree of involvement. In the second place, it enables the physician in charge to judge which functions are impaired and to what degree. Further study may show that this particular tabulation is erroneous in some respects. However, it is hoped that it, or a similar table, may be used as a standard by which to judge of renal function. Other tests for changes in diseases of the kidney might be plotted in on the same scale. It should be clear that no functional test can be used as direct evidence for the diagnosis of the anatomic or etiologic type of disease present, or even as a therapeutic guide, but only indirectly as an assistance to the experienced in arriving at a final judgment. A low hemoglobin percentage, for instance, gives an exact measure of the degree of anemia present, but tells nothing of its cause or of the exact treatment indicated.

TECHNIC EMPLOYED

The phenolsulphonephthalein test of Rowntree and Geraghty was performed according to the method outlined by these authors.[10] The procedure of Folin and Denis[11] was employed to obtain the figures for nonprotein nitrogen of the blood.

10. Rowntree, L. G., and Geraghty, J. T.: Jour. Pharmacol. and Exper. Therap., 1909, i, 579; The Phthalein Test, Arch. Int. Med. March, 1912, p. 284.

11. Folin and Denis: Jour. Biol. Chem., 1913, xiv, 29.

The method of Marshall[12] was used for the quantitative determination of urea nitrogen in the blood.

In ascertaining the figures for Ambard's coefficient of urea excretion, the same method for blood urea was employed; the urea of the urine was estimated according to Marshall,[13] the coefficient itself was calculated according to the original formula of Ambard.[14] The test meal for renal function followed the technic as previously laid down by one of us.[9] The name of this test has been changed from "nephritic test meal" to "test meal for renal function," as suggested by Dr. L. F. Barker, since it has been employed in many other conditions besides nephritis.

GROUPING OF THE CASES STUDIED

Observations on over 200 patients are recorded in this series. The results obtained in cases of anemia, whether primary or secondary, are considered separately at the close of the article. This is done because anemia presents a condition whose cause for diminished activity of the kidneys can be definitely associated with abnormalities of the blood, and which furnishes one of the most clear-cut examples of dissociated involvement of the various renal functions. That is, the ability to secrete a concentrated urine is remarkably diminished, while the other tests show only slight if any depression of renal activity. There are other diseases, such as diabetes insipidus, which show similar characteristics. The interpretation of renal function in these as well as other abnormal conditions is quite impossible at present.

The remainder of the material has been grouped in various ways, intended to bring out certain points which study of the material has yielded. Because of lack of space, it is impossible to publish the tables in full.

GENERAL COMPARISON OF ALL THE TESTS EMPLOYED

A glance at Table 2 establishes the following facts:

1. The nonprotein nitrogen and urea nitrogen indicate a slighter degree of involvement of renal function than the other tests.

12. Marshall, E. K.: Jour. Biol. Chem., 1913, xiv, 283.
13. Marshall, E. K.: Jour. Biol. Chem., 1913, xv, 487.
14. Ambard: Compt. rend. Soc. de biol., 1910, lxix, 411, 506.

2. Phenolsulphonephthalein and Ambard's coefficient tend to show an equal degree of impairment of renal function.

3. The test meal for renal function demonstrates a greater degree of depressed function than the other tests.

The same relations hold true for each type of case when this whole group is subdivided into the following classes: hypertensive cardiorenal disease, passive congestion, nephritis without hypertension, and miscellaneous, which includes cases of prostatic hypertrophy, cystitis, polycystic kidney, etc. The significance of these findings will be discussed in greater detail in the remainder of the article.

TABLE 2.—DEGREE OF INVOLVEMENT BY THE TESTS AS COMPARED TO PHENOLSULPHONEPHTHALEIN, ACCORDING TO THE SCALE OF TABLE 1*

Degrees Variation from Phthalein	Nonprotein Nitrogen	Urea Nitrogen	Ambard's Coefficient	Test Meal
++	1 per cent.	1 per cent.	6 per cent.	15 per cent.
+	5 per cent.	10 per cent.	21 per cent.	35 per cent.
Same	48 per cent.	45 per cent.	47 per cent.	34 per cent.
—	32 per cent.	31 per cent.	23 per cent.	14 per cent.
— —	8 per cent.	10 per cent.	2 per cent.	2 per cent.
— — —	3 per cent.	3 per cent.	1 per cent.	
— — — —	3 per cent.			
Total cases....	85	162	156	136

* In this table, + signifies 1 degree greater involvement than that shown by phenolsulphonephthalein, and — 1 degree less. All the cases observed except those with severe anemia are grouped together in this table.

1. *The Nonprotein Nitrogen and Urea Nitrogen of the Blood, and Ambard's Coefficient.*—These three tests all determine the ability of the kidney to excrete nitrogenous waste products. Ambard's coefficient may indicate such an impairment of function even when the nitrogenous products in the blood are within normal limits.[15] In the present series (Table 3) this is readily observed. It also shows how slight increases

15. Ambard (Footnote 14). McLean, F. C.: Clinical Determination of Renal Function by an Index of Urea Excretion, THE JOURNAL A. M. A., Feb. 5, 1916, p. 415.

in the blood urea and total nonprotein nitrogen figures may be revealed in their true light by Ambard's coefficient, many of them evidently being due to renal insufficiency, while others are not.

TABLE 3.—COMPARISON BETWEEN THE DEGREE OF INVOLVEMENT OF RENAL FUNCTION, AS SHOWN BY THE NITROGENOUS PRODUCTS IN THE BLOOD, AND AMBARD'S COEFFICIENT

Degree of Impairment as Measured by Nonprotein Nitrogen and Urea Nitrogen	Total Number of Cases	Percentage of Cases Exhibiting the Given Degree of Impairment of Renal Function, as Indicated by Ambard's Coefficient				
		0	+	++	+++	++++
0	56	57	27	16		
+	64	17	28	50	5	
++	21	..	19	43	33	5
+++	9	..	..	11	56	33
++++	15	..	..	..	7	93

In all the cases quoted in this article, the basis of classification has invariably been the highest value for nonprotein nitrogen or urea nitrogen obtained. By these means, the dietetic influence has been in great

TABLE 4.—THE EFFECT OF A LOW PROTEIN DIET ON THE LEVEL OF THE NONPROTEIN AND UREA NITROGEN OF THE BLOOD

Before Low Protein Diet		After Low Protein Diet		Diagnosis
Nonprotein N Mg. per 100 C.c.	Urea N Mg. per 100 C.c.	Nonprotein N Mg. per 100 C.c.	Urea N Mg. per 100 C.c.	
26	17	16	7	Sec. Contr. Kid.
..	26	..	5	Chr. Diff. Neph.
36	..	30	..	Chr. Diff. Neph.
47	..	30	..	Chr. Diff. Neph.
97	61	22	15	Sec. Contr. Kid.
145	126	32	23	Sec. Contr. Kid.

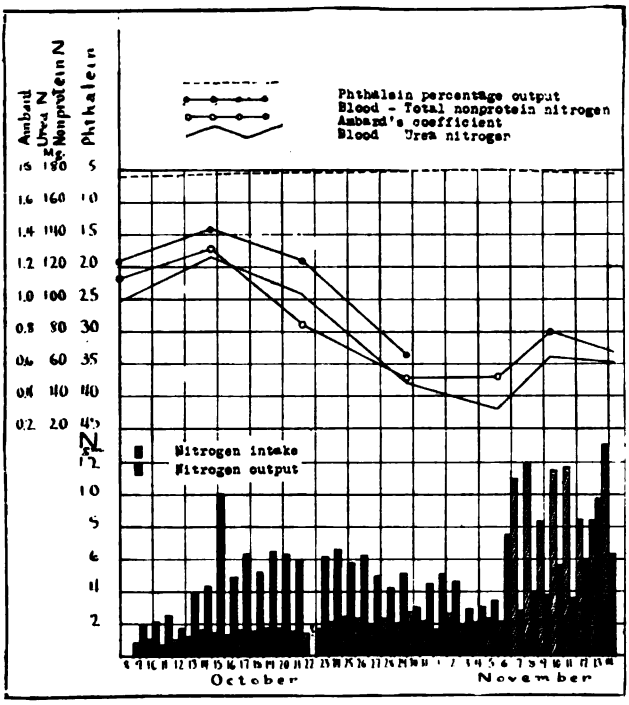
part obviated. It has been demonstrated what a great part diet plays in influencing the level of nitrogenous waste products in the blood.[16] Our experience has led us to the same conclusion, as may be noted in Table 4.

16. Folin, Otto; Denis, W., and Seymour, Malcolm: The Nonprotein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, Arch. Int. Med., February, 1914, p. 224. Frothingham, Channing, Jr., and Smillie, W. G.: A Study of Different Nitrogenous Diets in Chronic Nephritis, Arch. Int. Med., February, 1915, p. 204.

One of these cases is particularly noteworthy. The reduction of 145 mg. of nonprotein nitrogen to 32 mg. by dietary means is one of the most marked results of this kind thus far recorded. The partial data of this case are given in the accompanying chart.

The above and one other extrarenal factor must be borne in mind when blood nitrogen values are considered. This is the effect of an increased protein catabolism. It commonly occurs in the terminal stages of some forms of nephritis. That this condition in Bright's disease is not necessarily a rapidly fatal one is seen in this patient, who lived several months after these observations were made (see chart). Such a process may increase the blood nitrogen figures materially without signifying altered renal function as shown by the phenolsulphonephthalein or nitrogen excretion. It should, however, always be considered a serious omen, as may be gathered from those cases in whom we have observed it, all of whom have suffered a fatal issue either immediately or within a few months. Studies on these points are in progress at our clinic and will be reported in greater detail subsequently.

The chart shows how in the first two weeks of observation, in spite of a negative nitrogen balance, the nonprotein nitrogen of the blood varied but slightly, and how it subsequently dropped to a lower level. Considering the fact that this patient was taking a low protein diet with a large caloric value in starches and fats, it is believed that these figures indicate a protein destruction. This is confirmed by the fact that during the third week the drop in the blood values was much more rapid than during the second period, although the nitrogen loss was somewhat less. During this time, the protein destruction had evidently subsided. (The drop to 32 mg. of nonprotein nitrogen recorded in Table 4 occurred at a later period not included in the chart).



Data from a case of secondary contracted kidney, including the processes of protein destruction and assimilation and their relation to tests of renal function.

The last eight days of observation (see chart) indicate a marked retention of nitrogen without a corresponding increase in the urea nitrogen of the blood. This nitrogen was doubtlessly assimilated by the tissues. This series of events demonstrates how a nitrogen balance between the intake and the output in the feces and urine are not as valuable tests of the kidney's ability to handle a given amount of protein food as the blood determinations and Ambard's constant.[17]

TABLE 5.—RAPID CHANGES IN THE LEVEL OF THE NONPROTEIN NITROGEN OF THE BLOOD, DUE TO KIDNEY INSUFFICIENCY ALONE OR COMBINED WITH AN INCREASED PROTEIN CATABOLISM

Nonprotein Nitrogen of the Blood, Mg. per 100 C.c.		Days Between Observations	Diagnosis
First Observation	Second Observation		
35	426	23	Acute exacerbations of chronic nephritis; protein destruction
49	111	12	Chronic nephritis; bronchopneumonia; protein destruction
96	192	11	Chronic nephritis; uremia; protein destruction
127	304	8	Chronic nephritis; uremia; protein destruction
178	292	18	Chronic nephritis; uremia; protein destruction
68	222	54	Acute exacerbation of chronic nephritis; retention only
81	184	5	Mercury poisoning; anuria; retention only

Very rapid increments may occur in the nonprotein nitrogenous constituents of the blood (Table 5) caused either by kidney insufficiency alone or combined with abnormal protein catabolism. Such sudden changes may invalidate many of the attempts to formulate averages for blood figures in any given type of nephritis; they also explain the low nitrogen values found in some instances a few days before death in uremia.[2]

17. Mosenthal, H. O., and Richards, A. E.: Interpretation of Positive Nitrogen Balance in Nephritis, Arch. Int. Med., February, 1916, p. 329.

THE EARLY DIAGNOSIS OF IMPAIRED RENAL FUNCTION

It has been shown (Table 2) that the test meal for renal function demonstrates a greater degree of depressed function than the other tests. This does not necessarily imply that it appears as the first sign of impairment. A better answer to this question can be obtained if only those cases (excepting the anemias) are compared in whom all tests were carried out (Table 6).

Table 6 shows that:

1. The tests in order of their positive appearance are: the test meal, phenolsulphonephthalein, Ambard's constant, urea nitrogen of the blood.[18]

TABLE 6.—COMPARISON OF DEGREE OF IMPAIRMENT OF FUNCTION IN SEVENTY-THREE CASES OF ALL CLASSES EXCEPT ANEMIA IN WHICH ALL THE TESTS WERE CARRIED OUT, EXPRESSED IN PERCENTAGE OF THE TOTAL FIGURES

Degree of Renal Involvement According to Scale	Phenolsulphonephthalein	Urea N of Blood	Ambard's Constant	Test Meal
0	18 per cent.	40 per cent.	32 per cent.	10 per cent.
+	45 per cent.	35 per cent.	22 per cent.	27 per cent.
++	12 per cent.	14 per cent.	25 per cent.	27 per cent.
+++	11 per cent.	4 per cent.	12 per cent.	7 per cent.
++++	14 per cent.	7 per cent.	9 per cent.	29 per cent.

2. A maximal involvement is most frequently seen in the test meal, less frequently in the phenolsulphonephthalein test and least often in Ambard's coefficient.

The second consideration will be discussed under prognosis. The first point, that the test meal gives the earliest positive indication of renal damage, confirms the observation made in Table 2. This fact admits of an explanation, which indicates very beautifully how in many cases the negative finding in the phenolsulphonephthalein and Ambard tests is more

18. Christian and his associates have also found the test meal to be the most delicate indicator of renal function. Christian, H. A.: Am. Jour. Med. Sc., 1916, cli, 625.

apparent than real. As others[19] have found, the present series contained some cases of chronic diffuse nephritis with an excessive phenolsulphonephthalein output (Table 7); besides these there were many instances of hypertensive cardiovascular disease exhibiting a similar phenomenon. All these patients also showed a very rapid elimination of urea, so that the figures for Ambard's constant were normal or subnormal.[20] These cases of overactivity in mild kidney lesions have been referred by Schlayer and his associates[21] to the excessive response evoked in an intact organ by the irritation resulting from inflammatory processes. As the lesions advance, the renal parenchyma becomes more severely damaged and exhibits a subnormal activity to the pathologic stimulus. The stage of overactivity is characterized by phenolsulphonephthalein excretions and Ambard's coefficients, which appear to surpass even the normal criteria as signs of renal insufficiency. However, it has a different effect on the test meal, since the kidney irritability expresses itself in an excess of fluid excretion which has the tendency to result in a nocturnal polyuria, and a fixation as well as a lowering of the specific gravity. It is for this reason that the test meal is so frequently the earliest sign of an involvement of renal function.

PROGNOSIS

The relationship between tests of renal function and prognosis in nephritis has been found to be very uncertain. The extrarenal factors, cerebral hemorrhage, myocardial insufficiency, intercurrent infections, etc., have caused a fatal termination so frequently as to put a greater emphasis on the physician's clinical judgment than on the interpretation of tests for renal

19. Baetjer, W. A.: Superpermeability in Nephritis, Arch. Int. Med., June, 1913, p. 593. Pepper and Austin: Am. Jour. Med. Sc., 1913, cxlv, 254. Sellards: Bull. Johns Hopkins Hosp., 1912, xxiii, 298.

20. These findings as well as similar ones in fever and hyperthyroidism will be discussed in full in a future paper by D. S. Lewis.

21. For a summary of these views, see Schlayer: Beihefte z. med. Klin., 1912, viii, 211.

function alone. In certain patients, degrees of impaired kidney activity are found which are ordinarily considered incompatible with life. These as well as others who exhibit uremia with apparently fair functional kidney processes go far to show that uremia and renal lesions are not entirely dependent one on the other.

TABLE 7.—CASES OF CHRONIC DIFFUSE NEPHRITIS AND HYPERTENSIVE CARDIOVASCULAR DISEASE SHOWING A NORMAL OR SUPERNORMAL RESPONSE TO PHENOLSULPHONEPHTHALEIN AND AMBARD'S COEFFICIENT, WHILE THE TEST MEAL SHOWS SOME IMPAIRMENT OF FUNCTION

Diagnosis	Phthalein, per Cent.	Urea N of the Blood, Mg. per 100 C.c.	Ambard's Constant	Degree of Impairment Indicated by the Test Meal
Chronic diffuse nephritis.....	71	18	0.064	+
Chronic diffuse nephritis.....	78	11	0.054	+
Chronic diffuse nephritis.....	80	12	0.070	+
Chronic diffuse nephritis.....	70	8	0.068	+
Hypertensive cardiovas. disease..	76	8	0.048	0
Hypertensive cardiovas. disease..	63	12	0.060	++
Hypertensive cardiovas. disease..	70	9	0.050	+
Hypertensive cardiovas. disease..	85	9	0.059	0
Hypertensive cardiovas. disease..	67	16	0.077	++
Hypertensive cardiovas. disease..	81	15	0.080	+
Hypertensive cardiovas. disease..	65	..	.....	++
Hypertensive cardiovas. disease..	75	..	.....	+
Hypertensive cardiovas. disease..	65	..	.....	+
Hypertensive cardiovas. disease..	66	..	.....	++
Hypertensive cardiovas. disease..	67	..	.....	+
Hypertensive cardiovas. disease..	65	..	.....	++

The most striking example of this kind in our series is H. S.; diagnosis, polycystic kidneys. In December, 1914, the total nonprotein nitrogen of the blood was 118 mg., the excretion of phenolsulphonephthalein yielded only a faint trace in two hours (Ambard's coefficient, if determined, would undoubtedly have been very high), and the test meal showed a maximal impairment of function (maximal specific gravity, 1.011; variation from the highest to the lowest specific gravity, 1 degree; a night urine of 1,290 c.c.). Fifteen months later (March, 1916), the phenolsulphonephthalein and test meal were unchanged, the blood nitrogen was 112 mg., and Ambard's constant 0.67. At present one and one-half years after tests which indicated an extreme impairment of renal function, he is working at his office every day.

A high nonprotein nitrogen (above 90 mg.) or a high urea nitrogen (of 65 mg. or higher) has been found to be the most reliable prognostic sign. Of eighteen such patients, fourteen died in the hospital or shortly after leaving it; of the other four patients, one is still in the hospital in a precarious condition, one is the case of polycystic kidney referred to above, one is a case of mercuric chlorid poisoning with recovery, and the last is a case of secondary contracted kidney who has followed therapeutic directions so closely that he may almost be said to have outlived his day. It is clear to the physician coming in contact with these cases of nitrogenous retention that a sharp line can be drawn between those suffering with increased protein catabolism and those who are not. An example of this kind has been given in detail. This factor when present almost invariably foreshadows an unfavorable prognosis; a retention, on the other hand, not coupled with an abnormal degree of protein destruction, may do very well (as the case of polycystic kidney mentioned previously). In the earlier stages of nephritis, the nitrogen of the blood is very likely to lag behind the other tests (Tables 2 and 6) and it has been shown how Ambard's coefficient is more reliable under these circumstances as a test of renal function.

In nephritis, whether of the chronic diffuse or of primary contracted type, an Ambard's coefficient of 0.20 or higher has usually been associated with a fatal issue within a few months at the most. Of 87 cases with an index less than 0.2, 63 were traced and 15 died, 7 of uremia and 3 of cerebral hemorrhage. Of 36 cases with an index above 0.2, 30 were traced and 24 died, 12 of uremia, 9 of myocardial insufficiency, and 3 of cerebral hemorrhage. It is only to be expected that the patients with a higher Ambard's coefficient should show a more unfavorable prognosis. However, here, as in the case of other functional tests, an infallible guide to prognosis is not demonstrated.

The test meal usually reaches a point of maximal intensity some time before the other tests. Uremia, or death from some other cause, may occur at these periods, and thus lend an aspect of greater prognostic importance to the test meal than it actually possesses. It may be used as a valuable guide to prognosis in conjunction with the other procedures, but an opinion of maximal impairment of function should not be given without them.

The phenolsulphonephthalein test in this series has yielded results which have not varied from those reported previously.[22] An output of less than 10 per cent. has usually, but not invariably, warranted an utterly bad prognosis; occasional instances of death from uremia have taken place with an excretion of the drug in the neighborhood of 50 per cent.

EXAMPLES OF "DISSOCIATED" RENAL FUNCTION

Up to the present, the most constant examples of this kind have been found among the anemias. A few of the results are given in Table 8. Case 1 typifies the test meal result in a case of severe anemia: a marked fixation of specific gravity at a low level, and a nocturnal polyuria, indicating a maximal degree of functional involvement. After transfusion, the specific gravity rises, but is still markedly fixed. As the blood returns to normal, the test meal tends to resume a normal curve (Case 2). Under ordinary circumstances the low fixed specific gravity is characteristic of anemia with a hemoglobin of less than 40 per cent. If the anemia persists over a long period, such results are obtained even when the hemoglobin assumes a higher level. This fact, coupled with the progressive diminution of phenolsulphonephthalein in Case 4, would indicate that anemia in itself may have a harmful effect on the kidney.[23] Cases 3 and 4 are

22. Thayer and Snowden: Am. Jour. Med. Sc., 1914, cxlviii, 781.

23. Cases of anemia with serious functional disturbances of the kidney have been reported by Tileston, W., and Comfort, C. W., Jr. (Footnote 3).

TABLE 8.—THE RESULTS OF TESTS FOR RENAL FUNCTION IN PRIMARY AND SECONDARY ANEMIAS

Case	Phthalein per Cent.	Ambard's Constant	Urea Nitrogen Blood, Mg. per 100 C.c.	Test Meal for Renal Function								Hb.	Red Blood Cells	Diagnosis
				Night Urine		Sp. G. in the Two Hourly Day Specimens								
				C.c.	Sp. G.									
1	..	....	..	430	12	..	11	12	12	11	12	25	1,088,000	Pernicious anemia
				490	18	16	17	18	17	16	18	55	2,444,000	After transfusion
2	..	....	..	520	23	17	21	25	20	22	13	95	4,023,000	Pernicious anemia; splenectomy; repeated transfusions
3	55	0.10	13	990	09	09	08	09	10	10	10	52	2,816,000	Secondary anemia for longer than 9 months
4	73	....	..	1,250	10	14	10	10	10	11	11	39	2,464,000	Secondary anemia for long period
	42	0.04	6	395	10	09	10	09	10	09	10	50	2,320,000	One year later
5	54	0.09	14	415	14	..	22	25	15	19	12	50	2,000,000	Primary anemia
6	54	0.06	14	455	21	16	16	17	18	18	18	48	1,980,000	Primary anemia
7	46	0.06	10	740	14	22	16	18	16	15	11	40	1,880,000	Secondary anemia

examples of complete dissociation of function, the blood urea, Ambard's coefficient and phenolsulphonephthalein indicating only a slight or no impairment of function, the test meal a maximal one, whereas, in Cases 5, 6 and 7, with higher percentages of hemoglobin, the test meal reveals a slight or moderate involvement, as compared to the normal or slightly impaired state of the other tests.

The causes for extreme variance between urea nitrogen and nonprotein nitrogen of the blood and the other renal functional tests have been discussed. These tests are comparatively simple in their interpretation, and illustrate what great advances can be made when other problems can be attacked from a rational pathologic physiologic basis.

Occasionally cases are found in which there is extreme divergence of some of the tests, as in the following: In a woman, aged 37, the phenolsulphonephthalein excretion was 45 per cent. Ambard's coefficient 0.142, the nonprotein nitrogen of the blood 17, the urea nitrogen 9, and the test meal revealed a maximal involvement, as indicated by a low, fixed specific gravity. On first sight, this might be supposed to be a case of diabetes insipidus, as indicated by the low specific gravity and very moderate polyuria. However, such patients do not have a diminished phenolsulphonephthalein excretion,[24] and closer investigation of the nitrogen excretion, as suggested by a moderately impaired Ambard's coefficient, revealed the fact that the maximal involvement indicated by the test meal in its low fixed specific gravity was present because this individual did not have the power to concentrate nitrogen above 0.2 per cent. The salt output was much better than this.

Such cases illustrate how each test has its own significance, which, if thoroughly appreciated, may lead to marked improvement in therapeusis.

24. Fitz, R.: A Case of Diabetes Insipidus, Arch. Int. Med., November 1914, p. 706.

SUMMARY

1. A scale of impairment of renal function is proposed, according to which the tests may be measured. Such a graduation calls to the attention of the clinician the relative degree of involvement as shown by different procedures. Inasmuch as each of them has a significance apart from the others, comparison according to this method is an extremely valuable aid in the treatment and prognosis of diseases of the kidney.

2. The level of the nonprotein and urea nitrogen of the blood must be estimated largely as the resultant of three factors—kidney efficiency, diet and protein destruction. In judging of prognosis, when these substances are high in the blood of nephritics, due regard must be given as to whether their accumulation is brought about by retention alone or through retention coupled with protein destruction. The former offers a comparatively better prognosis than the latter.

3. The coefficient of Ambard is a better method of determining the ability of the kidney to excrete urea than the level of this substance in the blood.

4. The progress of renal disease is probably followed most minutely by means of the phenolsulphonephthalein excretion and Ambard's coefficient, as these tests furnish figures in which even small variations are of significance.

5. The test meal for renal function, of the tests employed, gives the earliest indication of diminished kidney efficiency. It likewise reaches the maximum degree of impairment before the others.

6. Each test for renal function covers only a limited range of the kidney's activities. It is, therefore, a mistake to speak of any test as measuring renal function as a whole. The aim should be to develop a proper interpretation of the old tests and easily applied new ones, in order to obtain a true guide to the treatment of diseases of the kidney.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. FOSTER, CHACE AND MYERS, MOSENTHAL AND LEWIS

DR. HENRY ASBURY CHRISTIAN, Boston: Dr. Foster has given us a very valuable analysis of the various types of uremia, one which I am sure will be helpful not only in a better understanding of the condition but also one that will give us a better idea of how to treat nephritic cases when confronted by the picture of uremia belonging to one of these various types. Dr. Chase has dealt chiefly with one method of testing renal function and his results are of decided value in comparison with other methods. Dr. Mosenthal has made comparisons of several methods and has drawn certain conclusions. This fact stands out in the symposium, that from the various methods we may get various results and we meet with cases in which we get individual variations from anticipated results though usually results from different methods agree very well. The important thing is that unless we apply more than one method we will miss evidences of disturbed renal function in some cases. The results of the studies we have conducted at the Peter Bent Brigham Hospital in Boston are analogous to those of Dr. Mosenthal in regard to the relative results of the several tests. Like Dr. Mosenthal, we have come to think that Ambard's coefficient is of more value than the urea nitrogen in the blood. McLean's method of expressing the relationship between the urea in the blood and the urea in the urine is better in our opinion than the Ambard method. We have in our work come to the conclusion that in the determination of the total nonprotein nitrogen no more light is thrown on renal function than by the determination of the urea nitrogen in the blood. This latter determination is part of the data required for the McLean index or Ambard coefficient and so adds no extra work. In addition, the dietary test as outlined by Dr. Mosenthal is of value particularly in the early cases of nephritis in that it will show disturbances at a period before the phthalein, urea nitrogen or other tests will. The results obtained with the dietary test are of great value but chiefly in the early stages of nephritis. In the later stages, however, it gives little additional information to that obtained from the phthalein test, the blood urea and the Ambard or McLean index. This is due to the fact that it shows its maximum effect relatively early in the nephritis and in the late stages changes but little with progress of the lesion.

DR. L. F. BARKER, Baltimore: I should like to emphasize two points. First, the kidney behaves differently as regards different substances. If we wish to know in a broad way what the renal function is, we must test the power of the kidneys to excrete several different substances. This requires much work. For instance, the chlorids may be retained by kidneys that are able to excrete nitrogen well, and *vice versa*. Second, the kidneys begin to eliminate certain substances as

soon as they appear in the blood, whereas other substances must reach a certain degree of concentration in the blood before the kidneys begin to eliminate them. Thus urea is a substance that is at once given out. On the other hand, the chlorids must reach a certain degree of concentration in the blood before the kidneys start excreting chlorids—the so-called threshold of chlorin excretion. The chlorids may fail to appear in the urine in pneumonia; the reason is that the blood-concentration in chlorids falls below the threshold of excretion. We must, I think, pay more attention to such excretion-thresholds.

What may the general practitioner use as tests of renal function? Of the several tests referred to there are two that are especially advantageous. First, the renal test diet as modified by Mosenthal is simple and easy to apply. The urine is collected every two hours. Even if we determine only the quantity and the specific gravity of each specimen thus obtained we can draw valuable inferences regarding the ability of the kidneys to excrete a concentrated urine and regarding the "fixation of the specific gravity" or a so-called hyposthenuria. Second, the phenolsulphonethalein test is a valuable and practical test, especially for the surgeon who desires to know whether the renal function is good enough to permit him to perform an operation. If the general practitioner would apply these two tests in special cases he would reap the many benefits derivable from the studies of renal function as far as they have yet gone.

DR. ALBION WALTER HEWLETT, Ann Arbor, Mich.: The tests that have been discussed give the same sort of information concerning the function of the kidney and the question arises as to which is the most easily performed and is at the same time reliable. As between the blood urea and phthalein tests we have found the former a more accurate indication of serious renal damage. The phthalein test, however, is the more easily performed and is, as a rule, sufficiently accurate. The information given by such tests is of great value in prognosis and similar information cannot be obtained by the usual urinary examinations. Dr. Foster has pointed out that in one type of uremia the symptoms are due to a retention of urinary products in the body. In our experience this is the commoner type of uremia. In order to determine what rôle, if any, urea itself plays in producing the asthenic symptoms present in this toxemia, Gilbert, Wickett and myself took large quantities of urea by mouth and raised the urea in our bloods to 200 mg. per 100 c.c. or over. When the urea in the blood exceeded 160 mg. asthenic symptoms occurred. There was no rise of blood pressure and no loss of appetite. From these experiments we are inclined to believe that urea itself is responsible for some of the manifestations of this type of uremia.

DR. H. J. LEHNHOFF, Lincoln, Neb.: It appears to me that the result of this experimentation depends on a certain number of variables of the majority of which we have no knowledge and of even more of which we have absolutely no control. Some of these known variables might be illustrated by chronic infections, slight temperature elevation, conditions of the blood, abnormalities of the internal secretions, etc. These variables have an influence and I do not believe we should look on these abnormalities as being absolutely results of kidney pathology alone.

DR. NELLIS B. FOSTER, New York: I did not refer to Dr. Hewlett's experiment on himself as I believed he would speak of it. If he had sought my advice regarding doing it on himself, I would have told him not to do it, although it is an experiment I have wanted to see done. According to my notion, such amounts of urea would be dangerous should the kidney function be imperfect, but I rather doubt that urea is the sole factor productive of symptoms with the asthenic type of uremia.

DR. A. F. CHACE, New York: General practitioners wish to know those tests which are of practical value and those which are of academic interest. The examination of the blood requires only from 1 to 10 c.c. of blood and is comparatively simple. The advantages of these tests are that the physician does not have to pay attention to prepared diets and to specimens of urine carefully collected. I wish to recommend as practical tests, the estimation of the uric acid, creatinine, sugar and the CO_2 combining of the blood.

DR. HERMAN O. MOSENTHAL, Baltimore: A very important point is the relation of extra renal factors to kidney function. When we speak of renal function we mean the eliminative power of the kidney. This is dependent not only on the condition of the kidney itself, but likewise on the almost innumerable other factors which may influence the activity of this organ, such as the food intake, the metabolic activities of the body, the composition of the blood, the blood pressure, the rate of blood flow, fever, etc. It is necessary to recognize the fact that renal function is frequently as dependent on the changes which occur in the heart, the gastro-intestinal tract, the blood, etc., as it is on changes in the kidney itself. It may be the appreciation of this fact that has led clinicians to apply themselves to the study of function rather than to the pathologic anatomy of kidney lesions. In taking up studies of this kind, we are working with a twofold end in view: first, to obtain a greater insight into the patient's condition, and thereby to aid therapeusis, and, second, to increase our knowledge of the physiologic and pathologic-physiologic activities of the kidney. Contributions of great value have been made by the clinician to our knowledge of the functions of the thyroid, as well as other organs, by these means, and it is hoped that the same may be accomplished for the kidneys.

ELECTIVE LOCALIZATION OF BACTERIA IN DISEASES OF THE NERVOUS SYSTEM

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Many bacteria retain for a long time the peculiar properties which determine their characteristic localization. The importance of studying the infecting power of some in which these properties are less fixed has not been sufficiently considered.

Some years ago I showed that the common occurrence of endocarditis in animals following intravenous injection of a staphylococcus from endocarditis and numerous strains of *Streptococcus viridans* from chronic infectious endocarditis depended to a certain extent on clump formation, and that simultaneously with the disappearance of this property, both from artificial cultivation and animal passage, endocarditis failed to develop.[1]

The importance of making injections soon after isolation of the bacteria was emphasized at that time. In 1909 Lewis and the writer[2] reported the isolation of a diplococcus from the thrombus in the portal vein in primary portal thrombosis, which produced retrograde thrombosis in radicles of the portal vein in a rabbit following intravenous injection. The full significance of the results of the animal experiments, however, was not realized at the time.

1. Rosenow, E. C.: Immunological and Experimental Studies on Pneumococcus and Staphylococcus Endocarditis, Jour. Infect. Dis., 1909, vi, 245; Immunological Studies in Chronic Pneumococcus Endocarditis, Jour. Infect. Dis., 1910, vii, 429; Further Immunological Studies in Chronic Pneumococcus Endocarditis, New York State Jour. Med., 1912, xii, 441; Experimental Infectious Endocarditis, Jour. Infect. Dis., 1912, xi, 210.

2. Lewis, D. D., and Rosenow, E. C.: Primary Portal Thrombosis, Arch. Int. Med., 1909, iii, 232.

During my studies on the transmutation of pneumococci and streptococci[3] in which relatively avirulent strains were made virulent by successive animal passages, and highly virulent strains less virulent by cultivation, marked changes in localization following intravenous injection in animals were noted. At certain lower grades of virulence, endocarditis, arthritis, cholecystitis, ulcer of the stomach, myositis and iritis, respectively, occurred, while when the virulence was high, hemorrhages and edema of the lung and bronchopneumonia commonly occurred. The latter observation is in accord with the results of Wadsworth.[4] The results suggested the possibility that diseases of widely different symptomatology might be due to strains of bacteria of the same or closely related species, but having peculiar localizing or infecting powers. Since then systematic cultures in which there was afforded a gradient of oxygen pressure have been made from diseased tissues in a series of diseases.[5] Streptococci frequently very sensitive to oxygen have been isolated in many instances from the involved tissues, often to the exclusion of other bacteria in rheumatic fever, arthritis deformans, appendicitis, ulcer of the stomach, cholecystitis, and myositis, and a diphtheroid-like streptococcus from the erythematous node in erythema nodosum. The streptococci from rheumatic fever and erythema nodosum especially showed a preference for partial anaerobiasis. Intravenous injection soon after isolation of these strains and commonly those from the respective focus of infection often showed a most marked tendency to localize electively in the tissues in animals corresponding to those involved in the spontaneous disease.[6] The lesions were

3. Rosenow, E. C.: Transmutations Within the Streptococcus-Pneumococcus Group, Jour. Infect. Dis., 1914, xiv, 1.

4. Wadsworth, A. B.: Studies on Pneumococcus Infection in Animals, Tr. Assn. Am. Phys., 1912, xxvii, 72; Pneumonia; a Bedside and Laboratory Study, Am. Jour. Obst., 1909, lix, 1080.

5. Rosenow, E. C.: The Newer Bacteriology of Various Infections as Determined by Special Methods, THE JOURNAL A. M. A., Sept. 12, 1914, p. 903.

6. Rosenow, E. C.: Elective Localization of Streptococci, THE JOURNAL A. M. A., Nov. 13, 1915, p. 1687.

truly elective in many instances. They approximated in type those of the spontaneous disease. The elective property or peculiar tropic condition of the streptococci in the foci of infection was undoubtedly an important factor in producing the diseases studied. The suggestion that other diseases whose etiology was still obscure might have a similar origin was at hand.

By the use of the same or similar technic, verification of the results in ulcer have been brought forward by Gerdine and Helmholz,[7] Hardt,[8] and Moody.[9] The results in iritis have been verified and extended by Irons, Brown and Nadler.[10]

In this paper I wish to summarize briefly the results of an experimental study of the possible etiologic relation of localized foci of infection, especially in and about the teeth and tonsils, to diseases of the nervous system. The technic used was similar to that previously described. Owing to the wealth of material at my disposal in the Mayo Clinic and the willing cooperation of the patients and the members of the staff, favorable cases were selected for investigation. Effort was made to obtain bacteria for cultures from the depth of the focus by expressing the infected material from tonsils with a laryngeal mirror, and by aspirating the infected pockets about teeth with a sterile pipet. In the former it commonly happened that abscesses were ruptured, even in tonsils which appeared quite normal on the surface. These were usually situated in the pole of the tonsils. Tonsillectomy and extraction of teeth were done when indicated.

The cultures for injection were usually incubated at 33 C. in tall columns of ascites-dextrose broth (affording a gradient of oxygen pressure), for from eighteen

7. Gerdine, L., and Helmholz, H. F.: Duodenal Ulcer in Infancy an Infectious Disease, Am. Jour. Dis. Child., 1915, x, 397.

8. Hardt, L. L. J.: The Secretion of Gastric Juice in Cases of Gastric and Duodenal Ulcers, Am. Jour. Physiol., 1916, xl, 314.

9. Moody: Personal communication to the author.

10. Irons, E. E., Brown, E. V. L., and Nadler, W. H.: The Localization of Streptococci in the Eye. A Study of Experimental Iridocyclitis in Rabbits, Jour. Infect. Dis., 1916, xviii, 315. The apparent inability of some to corroborate these and the results on the transmutation work appear explainable as due to differences in technic and differences in the character of strains studied.

to twenty-four hours, centrifugalized in the containers in which they were grown, the supernatant broth saved for filtration and for injection of animals, and the sediment suspended in sodium chlorid solution, so that 1 c.c. represented the growth from 15 c.c. of the broth culture. Animals of different species were injected, often in series, with doses ranging generally from 1 to 3 c.c. of the suspension for rabbits and guinea-pigs, and from 0.25 to 1 c.c. per kilogram of weight for dogs and goats. In many experiments smaller doses of the broth culture without centrifugalization were injected. In some the bacteria from emulsions of the tonsils and suspensions of the material expressed from the tonsils were directly injected.

Part of the material obtained from the patient was plated out and incubated on human blood agar, aerobically and anaerobically. Smears and inoculations on blood agar plates were made as a routine of the broth cultures and suspensions at the time of injection. In most instances the bacteria from the primary culture in the broth were injected. These cultures often contained a mixture of bacteria, but usually showed a great preponderance of streptococci and in some instances pure cultures of streptococci. While it was the rule to inject the bacteria from the primary cultures in broth, injections were made in some instances of pure cultures from single colonies on blood agar plates or from lesions and blood of animals. It is noteworthy how promptly the nonpathogenic or saprophytic bacteria disappear in animals.

The particular micro-organism responsible for the lesions in animals when mixtures were injected was determined by demonstrating its presence in the lesions and its absence in normal tissues (and blood) by means of cultures and sections, and by again producing similar lesions on reinjection of the pure culture.

In the table is given a summary of the results obtained in animals. The figures indicate the percentage incidence of focal lesions in the various organs.

ELECTIVE LOCALIZATION OF STREPTOCOCCI AND STAPHYLOCOCCI IN THE NERVOUS SYSTEM

Source of Bacteria	Strains	Animals injected	Appendix	Stomach or Duodenum, H.	Stomach or Duodenum, Ul.	Gallbladder	Liver	Pancreas	Intestines	Joints	Endocardium	Pericardium	Myocardium	Muscles	Kidney	Lung	Skin	Teeth	Nerve trunks	Meninges	Spinal cord	Brain	Dorsal roots
Multiple sclerosis	8	31	0	6	3	10	3	3	0	13	3	3	6	29	23	3	0	0	0	23	53	13	0
Sporadic anterior poliomyelitis	1	36	0	17	0	3	6	0	3	8	0	6	3	14	31	0	3	0	19	25	72	14	0
Transverse myelitis	1	21	5	24	19	0	0	0	33	14	14	10	14	24	10	10	5	0	5	50	67	24	0
Neuralgia	4	18	0	6	0	6	6	0	0	11	22	0	6	33	6	33	23	0	23	22	6	0	33
Multiple neuritis	1	19	11	11	5	5	0	0	11	22	5	16	11	27	16	32	0	0	70	0	5	5	0
Myositis and dental neuritis	1	24	0	13	0	3	0	0	0	4	13	0	4	71	13	0	0	50	46	0	0	0	0
"Myalgia"	12	29	3	10	14	3	3	0	0	46	24	0	23	83	17	3	3	0	7	7	3	3	0
Average incidence of lesions exclusive of specific strains			3	12	6	5	3	0	7	12	12	5	7	27	17	15	6	0	12	13	4	8	0

In a few instances the figures only approximate the actual occurrence of lesions in various organs because they were not looked for in all the animals injected, the pulps of only four to six teeth and approximately three fourths of the spinal roots were examined as a routine for lesions. Lesions in the liver, spleen, thyroid, lymph glands, tonsils, tongue, parotid, eyes and reproductive organs occurred so rarely that they are not included in the table. In the last line is given the percentage incidence of lesions in various organs exclusive of the specific strains. These figures serve as a basis for comparison. They correspond in a general way to those given in my previous table.[6] The incidence of arthritis, however, is less, while the incidence of myositis is greater. The latter is due to the frequent injection of slightly hemolyzing streptococci which commonly localize in muscles.

Lesions of the spinal cord, usually patchy in character, were observed in 58 per cent. of thirty-one animals injected with the bacteria from the tonsils or infected teeth in three cases of multiple sclerosis. In one of these the lesions appeared to be due to a staphylococcus; in the other two, to a green-producing streptococcus. Markedly increased reflexes, ataxia and paraplegia were noted during life in some of the animals. None became paralyzed. The duration of symptoms in the patients ranged from three to eight years. In two additional cases little evidence of local infection was found and the cultures failed to produce lesions in the spinal cord.

Lesions of the spinal cord, consisting of numerous hemorrhages, especially in the anterior horns in the cervical region, were noted in 78 per cent. of thirty-six animals injected with the staphylococcus from the tonsil in a typical case of sporadic anterior poliomyelitis. Many of these developed partial or complete paralysis, more marked in the anterior extremities, both after intravenous and intracerebral injection of pure cultures and of emulsions of diseased cords. Sev-

eral dogs showed marked improvement in motive power, and some obtained a complete restoration of movement. The lesions in the cord are quite different from those in epidemic anterior poliomyelitis.

Lesions of the meninges and spinal cord occurred in 50 per cent. and 66 per cent. of twenty-one animals injected with the bacteria as isolated from the pyorrheal pockets and tonsils in a case of transverse myelitis with paralysis of the lower extremities. Partial or complete paralysis, which began in the hind extremities, developed in many of these animals. The lesions of the cord consisted chiefly of hemorrhages both in the gray and white matter and of leukocytic infiltration in the meninges and surrounding the blood vessels.

The occurrence of the two types of paralysis, following injection of the bacteria from these two cases, was a striking picture. It was difficult, and in some instances impossible, to demonstrate bacteria in the areas of hemorrhage showing little or no leukocytic infiltration in the substance of the cord. They appeared to be infarctions from partial or complete thrombosis of the small blood vessels remote from the area of hemorrhage. This was true alike following injections in multiple sclerosis, anterior poliomyelitis and transverse myelitis. The bacteria were found in large numbers in the areas of infiltration in the meninges and surrounding blood vessels in transverse myelitis. These findings are in accord with the fact that bacteria are rarely findable in acute myelitis in man, and hence the lesions are thought to be toxic in origin or due to filterable viruses.

Lesions in or about one or more of the posterior roots occurred in 83 per cent. of eighteen animals following injection of streptococci from cases of brachial, intercostal and postherpetic neuralgia. The occurrence of neuritis in 28 per cent. of these animals is noteworthy. This and the high incidence of lesions in the skin, 28 per cent. (chiefly herpes), occurred in animals injected with relatively large doses. As far as can be

determined this is the first experimental demonstration of the probable nature of this form of neuralgia.

Lesions of the peripheral nerves occurred in 79 per cent. of the nineteen animals injected with the pneumococcus obtained on two occasions from multiple neuritis. In one rabbit typical wrist-drop developed. The animals seemed to be in pain. The lesions consisted of localized hemorrhages, edema and leukocytic infiltration, in which often many diplococci were found. The localization of the slightly hemolyzing streptococcus isolated from the dead pulp of a tooth and excised muscle from the neck in a case of myositis and dental neuritis was unique: 71 per cent. of the twenty-four animals injected showed myositis, 50 per cent. dental pulpitis, and 46 per cent. neuritis, chiefly of the dental nerves.

Lesions in or about the joints occurred in 48 per cent. of the twenty-nine animals injected, in the myocardium in 28 per cent., and in the muscles in 93 per cent., following injection of the cultures (all containing slightly hemolyzing streptococci) from the twelve cases of "myalgia" (cases of fibrositis or mild myositis, with or without periarthritis). These were included in this table to show the contrast in distribution of lesions and because in some cases it appeared that some of the pain was due to mild neuritis.

It must not be supposed that the lesions observed were slight or temporary, that they were always the result of the injection of large doses (even the small amount of exudate expressed from tonsils when directly injected was sufficient to produce the lesions in some instances), or that they were usually a part of a generalized fatal infection (62 per cent. of the animals recovered and were chloroformed for examination). Localizations strikingly like those in the patients were obtained in many animals of different species with the bacteria as isolated, but not with the same strains after cultivation for a time or after a number successive animal passages. In those strains

in which the elective property was marked, the characteristic localization occurred in nearly all the animals injected intravenously and in a high percentage of those injected intraperitoneally. Numerous strains from other sources and the filtrate of the broth cultures of the strains as isolated have failed to cause similar lesions. These and other facts preclude the possibility that the lesions in the animals were from spontaneous or accidental causes.

The conclusion seems warranted that the lesions in the patients studied were due to hematogenous infection from a focal source by the bacteria isolated. The improvement in symptoms following removal of foci of infection which were proved to harbor bacteria with peculiar localizing powers in multiple sclerosis, transverse myelitis, several cases of persistent neuralgia (although not in others), and in the case of dental neuritis and myositis speaks in favor of this view. The results emphasize the importance of thorough search for, and removal, if possible, of foci of infection in diseases of the nervous system. In the light of these results and much clinical evidences, as emphasized especially by Billings, a chronic focus of infection which cannot heal for mechanical reasons, often teeming with bacteria, must be considered as a test tube with a permeable wall embedded in the tissues, which, as I have already pointed out,[6] affords abundant opportunity not only for the entrance of bacteria and their products, but also the conditions favoring the acquisition of various infective powers by the bacteria. The demonstrated presence over a long period of time in foci of infection (particularly in chronic diseases) of bacteria with the same elective localizing powers suggests that the tendency to recurrences of a certain type of disease in the same patient and even hereditary tendencies may be due in part to the peculiar environment furnished by the individual which may favor the acquisition and maintenance by the bacteria of a particular infecting power.

Too much benefit should not be expected from the removal of evident foci of infection, because a similar condition may be present in inaccessible foci and in others too small to be detected. Moreover, recovery may be made difficult by local tissue sensitivity or peculiar mechanical conditions, and living bacteria in a metastatic lesion may continue the process independently of the focal source. In the case of dental neuritis and myositis the focus was found in the pulp of a dead molar tooth, no demonstrable lesions being found in the jaw. The removal of the tooth, while helpful, was not followed by the prompt disappearance of the symptoms. Streptococci demonstrated in sections of the excised muscle from the neck were proved alive ten days after a typical recurrent attack of spasm and pain.[11]

I wish here to express my thanks to the members of the staff of the Mayo Clinic (particularly Dr. Sheldon) for their willing cooperation.

ABSTRACT OF DISCUSSION

DR. FRANK BILLINGS, Chicago: When one discusses the subject of localized infection he ought to know the particulars of it and discuss it from the side of an infectious organism and all that relates to it. One should also discuss the host and the reaction of the body. This, however, is neither the time nor the place. The organisms infecting the body invade us, living as parasites harmful or harmless to the host. The organisms may act directly on certain tissues, lodge in them, multiply and produce reactions which are not always the same. We have recognized that the pathogenic micro-organism may possess a tropism for tissues, but have not appreciated the importance of this principle of bacteriology. One may conceive that the agents infecting some particular tissue like a joint may gain tropism for that kind of tissue; and if isolated and injected into an animal the same tissues will be infected in the injected animal. The work that Dr. Rosenow has done is proof that tropism may be gained in the infected tissues. The *Streptococcus viridans* may have an elective affinity for the heart and at another time an affinity for muscles or joints. There are many things we cannot explain. There are certain biochemical

11. The details of the clinical histories and the experiments, a review of the literature, and a more detailed discussion of the significance of the findings, are reserved for separate papers.

changes that occur due to reactions of the organism in the tissues. The phenomenal work that Dr. Rosenow and others have done has been due to the fact that they were able to come in contact with the patients. They have been able to be at the bedside and to use the patients as material. The first work done by Dr. Rosenow was in the wards of the Presbyterian Hospital. We never removed tissues from a patient without his consent or request. In chronic conditions we may find many parasitic organisms in the tissues. They were disregarded and only strains were used that were proved to be pathogenic. Finally, we have come to know that many conditions formerly thought to be noninfectious are infectious.

Dr. Ernest Zueblin, Baltimore: Dr. Rosenow's demonstration of the tropism of muscular tissue against certain bacterial strains may give us an explanation why we so frequently find the muscular system affected. For the clinician, the physician interested in dispensary work and the routine practitioner the frequency of chronic myositides, of interstitial infiltrations and nodosities encountered in the larger muscles (neck, etc.) is striking. Although among Swedish and Dutch physicians this type of muscular rheumatism is well known and successfully treated, among the general practitioner such findings obtained only by a careful physical examination are too often neglected. We all are aware of the tedious task to improve these chronic ailments, which left alone get worse and result in permanent injury. Any new experimental data in the line of Dr. Rosenow's work, showing an affinity of bacteria toward the muscular elements, must be followed with great interest as a possible way for better diagnosis, prognosis and treatment of such ill defined cases. From the experimental standpoint I would like to ask Dr. Rosenow if there is any possibility to increase that tropic affinity of the bacteria by the addition of certain organ extracts to the culture media, and if such a thing is possible what percentage of organ extract is permissible for obtaining the best culture result.

Dr. Samuel James Meltzer, New York: Dr. Rosenow's observations are certainly very striking and probably practically important. They are so striking that a great many bacteriologists and clinicians look at them with some suspicion. But Dr. Rosenow is in the fortunate position that the minority which believes in his results is composed of men who had the chance to see his experiments. The question is: how can it be explained that infections, localized in various organs, could be specifically produced by one and the same type of an organism, namely, by the streptococcus. Various explanations occurred to my mind. In the first place, that streptococci which may look alike and which may give even certain similar reactions, may nevertheless be fundamentally different. There are a great variety of species or

sub-species among the streptococci; we only do not yet possess the means of recognizing their individualities. That would mean that, for instance, infections of the appendix and gallbladder, etc., are really produced by definitely different sub-species of streptococci. A second explanation may be the assumption that the streptococci are merely constant companions of certain specific organisms, not yet known to us; the discovery of the ameba as the cause of pyorrhea alveolaris is an illustration. There is a third possible explanation. It is based on the conception of the *locus minoris resistentiae,* the importance of which in pathology was impressed on me some twenty years ago in experiments carried out by Dr. Cheesman and myself. We found then that the intravenous injection of organisms, streptococci, for instance, had hardly any influence on the experimental animals. However, we could find at any place in the animal body the specific organisms in pure culture when we, previous to the injection, caused a slight lesion in that place. We thus localized these organisms in circumscript places: the liver, the parietal peritoneum, the uterine mucosa, etc. Now the *locus minoris resistentiae* may be considered from two points of view. One is that locality possesses a diminished resistance to *all* parasitic organisms; and the other is that this locality is less resistant to an organism which acquired a specific virulence for this tissue. It is the latter form of *locus minoris resistentiae* which I wish to apply to the observations of Dr. Rosenow. It is admissible to assume that specific organisms which are residing for a longer period in a certain tissue reduce considerably the natural resistance of this tissue to the virulence of that specific organism or rather increase the virulence of that organism to the specific tissue. When such an organism is now injected into a normal animal, that organism will show a greater virulence to the corresponding tissue in the new animal. It is, for instance, thus possible that a strain of streptococci which was obtained from a case of appendicitis acquired a higher virulence specifically to the tissues of the appendix. The intravenous injection of such an organism may, therefore, produce appendicitis and no lesions in any other organisms.

Dr. G. Canby Robinson, St. Louis: The elective localization of bacteria is an interesting conception, and has a very important bearing on the question of etiology of disease. Many of the conditions that have been discussed by Dr. Rosenow have a nonspecific etiology, the localization of the infection rather than the type of organism being responsible for the disease produced. But this theory should not be made to play a rôle in the causation of diseases resulting from specific infections. Surely Dr. Rosenow does not believe, for instance, that he has produced true acute anterior poliomyelitis in animals by injecting a streptococcus or staphylococcus which he obtained from the tonsils of a patient with

this disease. It is fair to claim that the organisms infected, localized in the cord and meninges of the animals, but this localization does not constitute poliomyelitis as the term has been adopted to apply to a definite, clear cut clinical entity, caused by a filterable virus quite different from bacteria of the ordinary type.

DR. HENRY ASBURY CHRISTIAN, Boston: In analyzing the remarkable work of Dr. Rosenow we can make something like this subdivision: There are groups of cases with local lesions from which local lesion organisms can be isolated and when injected into animals these organisms localize in them at the same place from which they were isolated in the patient. From the appendix, in appendicitis, organisms may be isolated and if injected into animals they localize in animals at the same place in a predominating number of cases. It seems to be like the homing instinct of pigeons. Then there is another group of cases which present this difference. They are cases in which the organism is isolated from a focus that is not a part of the disease. The organisms isolated from such a focus if injected into animals localize themselves not in tissues which are similar to the tissues from which they were isolated but in tissues corresponding to the tissues involved in the general disease. This applies in Dr. Rosenow's case of multiple sclerosis, a disease of the central nervous system. Here the organisms are isolated from the tonsil but in animals localize in the central nervous system. I should like Dr. Rosenow to give us some idea why it is that an organism isolated from the teeth or tonsil will localize in the central nervous system rather than in the tonsil or teeth. These are two groups of cases which cannot be explained directly in the same way. In the second group the organism maintains the quality of localizing when injected into animals in certain tissues although it has not been localized in the body of the patient in that particular place. In cases of multiple sclerosis the organism must have been long present in the patient's tonsil without losing its power of localizing in the central nervous system. In conclusion I would like to express my appreciation of the tremendous amount of experimental work that Dr. Rosenow has done and which has thrown much light on this subject.

DR. EDWARD C. ROSENOW, Rochester, Minn.: The importance of injury from accidental causes as a determining factor in localization of bacteria as raised by Dr. Meltzer, is fully appreciated. The nature of the lesions observed, their location, and the incidence of their occurrence, as well as the care and individual caging of animals, precludes the possibility that injury from accidental causes had anything to do with the localization of the bacteria in these experiments. The "warning note" raised by Dr. Robinson is, I feel, superfluous, but it gives me opportunity to emphasize that the

case of anterior poliomyelitis was not of the epidemic type, but sporadic anterior poliomyelitis, and that the elective property or peculiar tropic condition of the bacteria is, of course, only one of a number of factors determining their localization. Dr. Christian's questions are much to the point. I have repeatedly emphasized the fact that the bacteria having elective properties in the diseases which I have studied, do not usually produce inflammation of tonsils sufficient to cause subjective symptoms of tonsillitis, and that when the diseases studied occur in association with tonsillitis, they occur commonly some time after the height of the attack. The pus or other exudate containing the bacteria having elective affinity is not from actively inflamed tonsils, but usually from small atrophic tonsils with deep pockets which cannot heal for mechanical reasons, and which are virtually test tubes with a permeable wall. The bacteria in these tonsils are virtually outside the tonsil and, hence, should not be expected to localize in the tonsils of animals. It is impossible to say definitely at present on what factors the acquirement of elective properties depends. Chronic foci of infection, such as the above, however, appear to furnish conditions favorable not only for the entrance of bacteria, but for them to acquire varying infecting powers. It was thought more important to determine first to what extent localization of bacteria depended on peculiar properties of the microorganisms at hand, and then to study more closely the exact mechanism involved. This study is now in progress. While other factors, such as varying degrees of resistance and other peculiarities in animals normally present or produced experimentally, are of importance in determining localization of bacteria, it appears from this study, in which due regard is paid to the question of oxygen pressure, the proper nutrition and the early injection of animals, that the diseases studied are due in some instances to common pathogens, but which have acquired peculiar infecting powers.

THORACIC DISEASES

THE STATUS OF SURGICAL THERAPY

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In addressing, single handed, a group of practitioners of internal medicine, I realize that I do so at my own risk. I beg your indulgence, however, for my theme is one which vitally concerns us all.

The treatment of diseases of the lung, pleura and mediastinum is in a lamentably chaotic state. Much has been written on the pathology, bacteriology and clinical picture of thoracic diseases. But what are we doing which is curative for the mortals thus afflicted? Are we not grossly incompetent? Is it not probable that more cooperation between the internist and surgeon might result in better treatment of the patient? Is the surgeon operating on lesions which the practitioner might cure? Is the practitioner treating some patients unsuccessfully whom the surgeon might cure? Are we sufficiently familiar each with the other's more recent advances in therapy? Or have we perhaps made no advances?

The thoracic cavity is too treacherous a region to become the scene of pastime surgery. The thorax surrenders all playground titles to the pelvis.

Surgery of the pleura begins only at the point where nonoperative treatments have failed. Duodenal ulcer may respond to both surgical and medical treatment. Both will be employed. Not so of lesions of the thorax. No surgeon will be fool enough to enter the chest until his "angel brother" internist fears to tread further without success.

No region in the body demands the combined efforts of physician and surgeon more than the pleural cavity. The internist occasionally needs the surgeon, and the surgeon never ceases to require the conservative help of the physician. Therefore, kindly regard us thoracic surgeons as your servants rather than as your substitutes, as your consultants rather than your competitors.

If we are to be your servants we must convince you that we are neither presumptuous, bold nor boisterous, but rather cautious, conservative and conscientious.

You will find us useful and safe in the treatment of postpneumonic abscess. We are not unmindful of the high percentage of spontaneous cures by bronchial drainage alone. We urge, however, the privilege of early consultation that we may aid in determining the point at which spontaneous recovery is doubtful and at which the operative risk begins to increase. In such cases, ours is a record of extremely low mortality.

In chronic lung abscesses we are less successful. We drain single abscesses and overlook others. We allow our drainage tubes to produce lung necrosis and fatal hemorrhage. We would welcome the exclusion of this group of cases from the surgical field. We watch with interest your efforts with vaccines, climatic influences and hygiene, but we grieve at your limited accomplishments.

We believe that early compression therapy in chronic abscess cases will do great good. If you are unsuccessful in collapsing the infected lung with artificial pneumothorax, we would much prefer to operate to strip adhesions, thus facilitating the collapse which you will maintain later, than to be requested at a late hour to perform a drainage operation in a thoroughly septic patient.

Bronchiectasis would seem to be a chronic, incurable disease. The records are hopelessly void of successes without surgery and painfully attended with fatalities by operation. We venture to suggest that the practi-

tioner withhold such patients with even more than his accustomed tenacity; not obstinately, however, but intelligently.

In true bronchiectasis, expectorants, inhalations, cough mixtures, climatic changes and vaccines fail. Artificial pneumothorax has been reported as curative. I entertain grave doubts as to the truth of such reports. Either the reported cases have not been true bronchiectasis or a cure has been claimed merely because of a considerable temporary reduction in the quantity of sputum. In three cases of bronchiectasis confined to one lower lobe I have packed the lower pleural cavity with many yards of gauze. A chronic empyema has been artificially produced with incarceration and compression of the diseased lobe. The quantity of sputum has been slightly reduced; otherwise the disease has continued unaltered. If such radical compression fails to obliterate the cavitations and to produce cicatrization, how much less will the intermittent maintenance of artificial nitrogen pneumothorax accomplish?

Further, do not invite or permit a surgeon to drain your case of bronchiectasis. He will do no good and possibly much harm.

Assuming the correctness of my contention that expectant treatment, vaccine therapy, artificial pneumothorax and drainage operations are valueless in bronchiectasis, we ask what can be accomplished with our present knowledge? In eight or nine cases out of ten, absolutely nothing which is curative. In the tenth case, however, with the process confined to one lower lobe in a young adult patient with good resistance, further consideration is to be entertained. Look on the pathologic condition of the diseased lobe as beyond hope of correction except by actual removal. Let no man attempt a lobe excision in a single operation. Your otherwise comparatively content and even efficient patient, if thus treated, will soon be dead. A single lobe of the lung may be removed safely in a three-stage or four-stage operation, which I have

described elsewhere. Within a year a small series of cases thus treated will be reported. The results so far are certainly most promising. Meanwhile we remain hopeful and open to conviction that internists will substitute a nonoperative cure; the surgery of bronchiectasis is at best treacherous and laborious, and, to say the least, filthy.

Emphysema is another stumbling block and again a chronic pathologic condition. Surgery offers but one operation, namely, the removal of several costal cartilages on one or both sides. It accomplishes increased mobility and expansion of an otherwise rigid thorax. In a considerable proportion of cases it relieves distressing symptoms. It does not cure. Heart and kidney complications and suppurative bronchitis are contraindications. Much reduced expansion is the sine qua non of indications. We have too few results on which to base definite opinions as to the value of this procedure, but inasmuch as it is comparatively safe, we urge you to submit cases that we may both know more as to its real significance.

To spare you the mortification of accusing us surgeons of incompetency in the handling of pleural empyema, I will make a series of confessions. Not infrequently we operate for acute empyema and fail to find pus at the very point at which you have recently located it with a needle. You may justly contend that our methods of exploring the pleural cavity are inadequate. If a finger thrust through an opening made by the removal of a half-inch of rib fails to strike pus, naturally you cannot be entirely satisfied that it is absent. Having urged the internist to prevent the occurrence of chronic empyema by the early detection of pus following pneumonia, we sometimes so badly handle an acute case that it is soon converted into a chronic case. We fail to place the drainage tubes at the bottom of the cavity. We either apply suction at the expense of drainage or we drain without providing for the expansion of the lung.

These and numerous other surgical errors it is well you should know. You have much to do with the post-operative conduct of empyemas and are justified in demanding that such surgical fallacies be corrected that your patient may more promptly recover. If an operative case of acute empyema is still draining at the end of eight weeks, do not remove the drainage tubes and trust to the Almighty; do not inject various pastes and solutions or administer vaccines until you have called back the surgeon. Point out to him that the Roentgen ray shows lack of lung expansion, introduce a probe and demonstrate the persistence of a considerable cavity. Remove a small piece of tissue at the mouth of the drainage opening, and have a section made and examined for tubercles. Be satisfied only by this procedure as to the possibility of a tuberculous empyema. (Cultures and guinea-pig inoculations from the purulent discharge will rarely prove the presence or absence of tuberculosis.) With such data at your command, the surgeon may admit that the delay in healing is mechanical. He may advise redrainage and freer drainage at a lower point. He should consider the advisability of opening the chest widely and freeing the lung of its adhesions to prevent such fixation as will otherwise result in a chronic empyema.

If despite all such further efforts an empyemic discharge continues four and five months, another surgical consultation is indicated. Probably then a decortication of the lung or some form of osteoplastic operation is indicated to obliterate the cavity. If such is done early when the ultimate necessity is obvious, healing may be complete in less than a year. It is criminal that these patients should be allowed to drift along with chronic sepsis into amyloid disease.

Vaccines may be employed to lessen the profuseness or foulness of drainage, but if designed as a curative measure necessary surgical measures will be detrimentally postponed. Bismuth and petrolatum should be used in very small cavities, and only when the need of further surgery is excluded.

Of course, the surgeon is essentially at fault in that he does not follow the progress of each patient with empyema whom he operates on in the acute stage, but I dwell on this subject of empyema to emphasize that surgery properly and persistently applied is the best, if not the only means of cure. After the primary operation the patients return to you, essentially, perhaps, because the surgeon neglects to follow their convalescence. Apologetically, therefore, we ask your assistance and urge you to demand further surgical intervention when the obliteration of empyema cavities is obviously not progressing.

In the management of tuberculosis, the practitioner has ceased to look to the surgeon for help. Ten years ago, when the experimental removal of large portions of the lungs of animals was first successfully executed, we wondered if such might be possible and feasible in tuberculosis in man. Thus far, however, such is not the case. The removal of the diseased lung of man is associated with obstacles not present in the excision of the normal lung of a healthy dog. Respiratory and circulatory disturbances occur in the process of intrathoracic operating which we are struggling to interpret and overcome, and in the diseased person these complications are exaggerated. The tuberculous patients is *a priori* a poor surgical risk and the outlook for successful extirpation of tuberculous lung tissue is particularly discouraging. You read of collapsing the tuberculous lung by an extrathoracic operation, pleuropneumolysis, or the resection of numerous ribs to collapse the chest wall and, therefore, the lungs. Let us suspend such radical and dangerous experiments until we have learned more of the actual value of collapse therapy by artificial pneumothorax. We surgeons may well await your developments with this harmless method before substituting a method that is dangerous. For the present, at least, in those cases in which adhesions prevent the introduction of gases

into the pleural cavity, let nature rather than ill-applied surgery take its course.

We do not regard the drainage of tuberculous cavities as a profitable surgical measure. At present writing the only justifiable mechanical procedure in pulmonary tuberculosis is collapsing the lung by the introduction of nitrogen or fluid into the pleural cavity. This treatment is carried on very properly by internists. Suffice it to say that collapse therapy has almost a specific effect in the arrest of pulmonary hemorrhage. In progressive cases with unilateral or even bilateral involvement, symptomatic relief can be expected in 40 per cent. of the cases in which collapse is conscientiously maintained. The disease is arrested in a considerable number of cases of the progressive type; 13 per cent. would not be an exaggerated estimate.

I am involved in the study of a group of cases which we have doubtless misinterpreted. We see swellings on the chest wall, generally on the anterior side. There is some fluctuation, but no redness or tenderness for many weeks. Eventually they rupture or are incised. They then discharge pus and finally a bloody, watery secretion. These swellings are called cold abscesses, tuberculosis of the ribs, and necrosis of the chest wall. Stereoscopic radiograms should be taken in each of these cases. One generally finds the shadow of a localized pleurisy in the region of the swelling. Operation performed as an excision or dissection reveals a minute fistulous opening between two ribs leading to the outer surface of the parietal pleura. The ribs are almost never necrosed. It is often impossible to find either bacilli or tuberculous tissue. Nevertheless, the conduct of the lesion in every way resembles that of a tuberculous process.

Drainage alone in these cases has no curative effect, and excision of the abscessed area alone is likewise inadequate. However—and here the internist's cooperation is imperative—free drainage or excision, plus the maintenance of the hygiene advised for tubercu-

losis, is the sole source of success. Either one is valueless alone, but in combination the healing of an otherwise chronic discharging focus may be effected. In other words, the treatment of the case as one primarily of tuberculous pleurisy, which time will prove to be the basis of such lesions, in conjunction with free abscess drainage, is the treatment of choice.

There are other swellings on the chest wall adherent to the ribs. These are tumors, either primary in the ribs and cartilages or extending to the tissues of the chest wall from the pleura or mediastinum, rarely from the lungs. Some practitioners are accustomed to regard such tumors as inoperable. I suggest the following routine in these cases: Examine the stereoscopic radiogram. Evidences of underlying pleurisy will suggest the tuberculous abscess just mentioned; to all external appearances these abscesses are identical at the beginning with tumors. Examine the ribs with the Roentgen ray; sometimes destruction of bone will confirm the diagnosis of malignant metastases. Study the mediastinal shadow. If there are lateral bulgings suggesting mediastinal tumor, the growth seen on the chest wall is inoperable. Lymphosarcoma is the probable diagnosis; Roentgen ray and radium are the only treatments. If, on the contrary, the intrathoracic Roentgen-ray findings are negative, an operable tumor confined to the chest wall may be confronting you. Myxochondrosarcoma of the ribs is the probable lesion. Radical removal of the tumor with the involved ribs may be performed with or without opening the underlying normal pleura. Pray do not consent to the dissection of such a growth from the ribs. It will recur. Permit only a total extirpation and see to it that despite assurances to the contrary by the surgeon, Roentgen-ray therapy is employed during convalescence. If such operations are thorough, a lively reaction is to be expected on the chart. Bloody fluid accumulates in the pleural cavity. These developments are to be expected, but are almost universally withstood, and recovery ensues.

Of all swellings on the chest wall, then, there are at least two types that are curable. A careful radiographic study of the case is imperative to determine the surgical possibilities.

In primary malignant disease of the lung itself surgery laments its incompetency. In the first or operable stages there are not sufficient symptoms to force the patient to seek medical advice. If roentgenograms are taken at the beginning of symptoms, a diffuse inoperable process may be detected. If a localized shadow is shown, it is misinterpreted generally as abscess or local pneumonitis. Expectant treatment in the hope of spontaneous drainage is employed. Meanwhile the disease progresses and at a late hour the cachexia of the patient reveals the probable diagnosis.

The removal of an early localized malignant tumor of the lung is surgically possible; but we cannot expect the internist to diagnose such tumors at the early stage. We, therefore, urge you to retaliate by ridiculing our unwillingness to perform exploratory operations within the chest as within the abdomen for diagnosis and for the determination of operability. The technic of such exploration has been perfected and yet it is not done. An exploratory thoracotomy should be a safe performance. Nothing will so promptly force us to more frequent explorations than the demands of our consulting internists.

The distressing predicament of persons with esophageal obstruction from carcinoma is a familiar picture. With the Roentgen ray and esophagoscope you make the diagnosis. Despite the recent admirable studies and investigations, the general surgeon seeks to avoid an operative fatality. In view of our present knowledge and results, we would again assure you of our conservatism. We are devoted essentially to seeking the maintenance of nutrition by early gastrostomy; second, we are learning to sidetrack the esophageal constriction, at the same time maintaining for the

patient the consoling function of swallowing food. The esophagus is brought to the surface at some point above the stricture. A new esophagus is manufactured from the greater curvature of the stomach and brought subcutaneously to the upper thoracic region in close approximation to the presenting proximal end. The two are sometimes successfully connected either by suture or tubing. Then, and not until then is intrathoracic extirpation of the exophageal cancer to be considered. Radium and the Roentgen ray are first to be employed, but within a few years more successful extirpation may be recorded. In consulting with a patient thus afflicted the internist is urged to bear in mind the value of early gastrostomy, the recent successes in intrathoracic esophagoplastic surgery and the possible value of intra-esophageal radium and extrathoracic Roentgen therapy.

My title is the present status of surgery of thoracic disease. He must indeed be an optimist who reads this story with any considerable enthusiasm as to the contributions which surgery at present affords. Should this paper be followed by an address detailing the results of expectant and medicinal treatment, you then would have listened to two sad stories instead of one. In view, therefore, of our individual incompetency, is it not imperative that our energies should be applied cooperatively that the much neglected thoracic region may become the scene of greater accomplishments?

ABSTRACT OF DISCUSSION

DR. WILLY MEYER, New York: Dr. Robinson's paper reflects the view I have held for the last eight years; namely, that if abdominal disease represents a true chapter of borderland troubles, then thoracic disease does this still more. Bronchiectasis is originally and principally an affection of the bronchi. As a matter of necessity the lung parenchyma will gradually become affected, just as the tuberculous process affects the bronchial system later on.

Regarding the etiology of the trouble, there can be no doubt that in quite a number of these cases the disease is due to aspiration, particularly during general anesthesia. If a patient then gets through the aspiration pneumonia, he is

still threatened with subsequent bronchiectasis; especially often is the latter complication observed after operations on tonsils or adenoids. For distinct localization, particularly in the early stages, the bronchoscope renders the greatest assistance. Today every hospital in which thoracic affections are treated ought to have on its staff a carefully trained, reliable specialist for bronchoscopy and esophagoscopy, a man who will conduct these examinations without doing harm to patients, and who is able to interpret what he sees. In the early stage a specialist may treat the case conservatively. The only cure for the advanced stage is extirpation of the diseased portion of the lung. We must learn to lessen the dangers of pneumectomy. At present a two-stage operation appears advisable. As to the surgical treatment of tuberculosis, it has been just in the patients, in whom, on account of adhesions between pulmonary and costal pleura, nitrogen-insufflation is impossible, that thoracoplasty in two or three stages has had its greatest triumphs in the hands of Sauerbruch and Wilms abroad. They were able to effect improvement or cure in 60 to 70 per cent. of consumptives, who under continued medical and hygienic treatment were hopelessly lost. Personally, I could well do extensive thoracoplasty (in bronchiectatics), under local and regionary novocain anesthesia; only now and then a whiff of a general anesthetic became necessary. So far it has been impossible in New York City to get tuberculous patients with cavity formation admitted to hospitals, but I still hope to overcome the difficulty. If anywhere, then here, internist and surgeon must work together. Regarding the diagnosis of esophageal affections: A patient who experiences difficulty in deglutition will always first consult an internist. Let the latter then remember, that, with the single exception of the presence of an aortic aneurysm, every one of these patients represents a surgical case. The paramount necessity for carcinoma is the early establishment of the diagnosis. Here the Roentgen ray, next to esophagoscopy, promises to become of greatest help to us.

Dr. Frederick T. Lord, Boston: As an internist I want to endorse the plea made by Dr. Robinson and by Dr. Meyer that the physician and the surgeon work together in these thoracic cases. Pulmonary abscess usually comes first under the observation of the physician on whom falls the responsibility of recognizing the nature of the process and the indications for surgical intervention. It should be appreciated that acute abscess is far more amenable to surgical treatment than chronic abscess and that by delay in the consideration of surgery a favorable opportunity for relief may be lost. Dr. Meyer referred to the frequency with which pulmonary abscess follows operation on the upper parts of the respiratory tract and this has recently impressed me also. Of 206 cases in our series, the pulmonary abscess followed the

removal of tonsils or adenoids, the extraction of teeth, operations on the nasal septum or about the mouth in nineteen—or about one in every ten cases. An interval of from one to four days usually intervenes between the operation and the onset of symptoms. The right lower lobe was involved in about one half the cases. Nine patients died. This is not the only field, however, in which surgery is to be accounted a contributing cause of pulmonary disease.

About one quarter of all deaths following operations under general anesthesia are due to lung complications of which bronchopneumonia and less often lobar pneumonia are the most common and serious. The aspiration of infected blood or tissue is the usual cause of pulmonary abscess following operations on the mouth or nasopharynx, and an acute infection of the respiratory tract existing at the time of the operation is responsible for a considerable proportion of the postoperative pneumonias. It is our duty to see that due consideration is given to the indications for operation in the acute cases lest we become responsible for the progress to a less favorable chronic stage of the disease. Spontaneous recovery is to be expected in only a small number of cases. It was noted in only five of 206 cases of pulmonary abscess in our series. The usual termination of acute abscess is either in death or in permanent damage to the pulmonary tissue. In the milder acute cases, in which the pulmonary lesion is small, without marked symptoms of sepsis, with purulent and not foul sputum, without a large amount of elastic tissue or lung shreds, the usual medical treatment under close observation with the surgeon may be tried for three to four weeks. In the absence of favorable progress at the expiration of this period operation should be considered. When, on the other hand, the abscess is large, accompanied by marked symptoms of sepsis and with foul sputum and abundant lung shreds a resort to immediate operation is imperative. Vaccine treatment of abscess seems to be a futile and irrational procedure. I cannot agree with Dr. Robinson that collapse therapy is a desirable procedure in chronic lung abscess or in the treatment of pulmonary hemorrhage due to tuberculosis. Sudden death from air embolism, collapse induration of previously uninvolved parts of the lung, and extension of suppuration from the lung to the pleura by rupture of adhesions are dangers which cannot be disregarded. To these dangers is added the almost even chance of compressing the wrong side of the chest in the attempt to treat hemoptysis due to pulmonary tuberculosis by this means.

Bronchiectasis is fortunately of rare occurrence, being noted in only about one in one thousand clinical cases and five in one thousand necropsy cases in our series. Isolated saccular bronchiectasis may be found unexpectedly and treated successfully surgically. When the bronchiectasis and complicating bronchopulmonary infection is sufficiently extensive to involve one or

more lobes of the lung, incision and drainage of a large cavity may ameliorate the symptoms. Pneumectomy and even lobe-excision are such desperate measures as to exclude them from serious consideration by any one anxious for other than relief or death. Regarding the treatment of acute empyema, immediate and free drainage of the pus is essential for prompt and permanent relief with the following exceptions. If the pus is sterile or contains tubercle bacilli alone, removal by thoracentesis is the procedure of choice and should be repeated at sufficiently frequent intervals to prevent the fixation of the lung in an abnormal position. Empyema complicating advanced pulmonary tuberculosis is also best treated by puncture. In patients who are gravely ill open incision and free drainage is often followed by a rapidly fatal termination and removal by thoracentesis is to be preferred as a preliminary to operation or as a life saving measure.

Dr. Samuel James Meltzer, New York: I would like to suggest the attempt to treat some cases of bronchiectasis by the following method. It is easy to introduce a tube into a bronchus, especially in that of the right side. Would it not be possible and advisable, when, for instance, the bronchiectasis is in the right lung, to introduce a tube as far as it will go, and then, after retracting it for about five millimeters, to inject a weak solution of nitrate of silver? The tube should have its opening at the end; it should not be a catheter. It may be advisable, before using the solution of nitrate of silver, to remove some of the pus from the cavity by blowing it out. The entire procedure, of course, would have to be repeated many times. I agree with Dr. Robinson that an exploratory thoracotomy, which may be followed by an operation, is indicated in many cases. I wish Dr. Robinson would tell us what he thinks of the practicability of my suggestion.

Dr. Samuel Robinson, Rochester, Minn.: In reply to Dr. Meltzer's suggestion as to the advisability of irrigating the bronchial tree with solutions such as silver nitrate: Of course we look on Dr. Meltzer as the authority in intratracheal insufflation, and while I have had no experience in irrigation therapy through the intratracheal tube, Dr. Meltzer would doubtless be interested to know the recent experience which I have had during the intratracheal anesthesia of a patient with bronchiectasis. Inserting the intratracheal tube in the usual manner, suction rather than insufflation was applied to the tube, removing purulent secretion throughout the operation. Meanwhile, the anesthesia was carried on by the drop method, the intratracheal tube coming out of the corner of the mouth under the mask. Fluid has been introduced into the bronchial tree and removed by suction, but as to the therapeutic value of this procedure in bronchiectasis, I do not know.

BRONCHIECTASIS OF THE UPPER LOBES

WITH REPORT OF FIVE CASES WITH NECROPSIES

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From etiology to treatment, the various problems which arise in connection with bronchiectasis are often a cause of difficulty. There are numerous theories as to its etiology, while as concerns the diagnosis, the figures of occurrence suggest that it is recognized twenty times more frequently by the pathologist than by the clinician. The difficulties of diagnosis are increased by the frequent association of bronchiectasis with conditions which may obscure, modify or conceal its features. But notwithstanding this, we should recognize bronchiectasis more often than we do.

SITE OF BRONCHIECTASIS

The older writers believed that the apex was the commonest site, but many modern authorities consider this erroneous and due to an imperfect differentiation of tuberculous and bronchiectatic lesions. Lebert, in a series of fifty-two cases, found unilateral upper lobe involvement in only 11 per cent. King found among the nontuberculous bronchiectases 33 per cent. unilateral and 67 per cent. bilateral, and among the tuberculous bronchiectases 46 per cent. unilateral and 54 per cent. bilateral. These figures indicate that while the tendency is to a bilateral involvement, the tuberculous cases show a greater number of unilateral cases. He found also that unilateral lesions were much

more frequent on the right side than on the left. Of our unilateral cases, one was on the right and the other on the left side. King found that for all types of bronchiectasis, tuberculous and nontuberculous, unilateral and bilateral, there is a marked preponderance of cases involving all the lobes of one lung except in tuberculous unilateral cases, in which he found no example of whole lung involvement. This is interesting in connection with our Case 3, in which unilateral involvement of the entire left lung was noted. When a single lobe was involved it occurred in the upper lobe only in a small percentage of cases of pure bronchiectasis, and in a somewhat greater percentage in the tuberculous cases. In other words, according to King, lower lobe involvement predominates strikingly in all types of cases, though to a less marked degree in tuberculous bronchiectasis. This is controverted by the necropsy figures of the Phipps Institute, Philadelphia, in which upper lobe involvement predominates in tuberculous cases. Our experience leads us to believe that while lower lobe involvement predominates in nontuberculous bronchiectasis, nevertheless, in tuberculous cases, upper lobe involvement is not infrequent.

The five cases here reported are unusual in the distribution of the bronchiectasis. They came to necropsy within a period of five months, and represent the only instances of bronchiectasis in eighty consecutive necropsies from the service of the Department for Diseases of the Chest of the Jefferson Medical College. Bronchiectasis involving the upper lobes alone is not common, and only slight reference to it is found in literature. These cases illustrate particularly some of the problems of diagnosis.

REPORT OF CASES

CASE 1.—*Extensive bronchiectasis with fibrosis limited to and involving the right upper lobe. Confusion with pulmonary tuberculosis. Differentiation. Death due to lobar pneumonia.*

H. D. No. E 4437, man, white, machinist, aged 62, was admitted March 30, 1915, and died Dec. 10, 1915. His past history was negative. There was no history of syphilis. During the last ten years he had suffered with a "winter cough."

Present Illness.—This dated to one year before, when he had a severe attack of bronchitis, which occurred in the middle of winter and gradually subsided in the summer, to recur during the winter prior to his coming under our observation. Shortly after the onset he brought up 2 ounces of blood during a paroxysm of coughing. The cough on admission was moderately severe and productive, during both the day and night, of a moderate amount of thick yellowish sputum. He never had any pain in the chest, but dyspnea occurred quite constantly on exertion. He had no chilliness, fever or night sweats. His best weight was 220 pounds at the time of onset, and the present weight 174 pounds. Coincident with the loss of weight there had been a gradual diminution in strength.

Physical Examination.—He was fairly well nourished. The chest showed some flattening of the upper right half anteriorly with slight drooping of the shoulder. The superficial veins over the right upper chest and anterior surface of the right shoulder to the middle third of the arm were dilated and tortuous. Expansion on the right side was distinctly limited. The percussion note was dull anteriorly on the right side from the apex to the third rib and posteriorly to the fourth vertebral spine. The breath sounds were generally harsh except over the area of dulness where, although their intensity was diminished, there was a distinct tubular quality. Vocal fremitus and resonance were increased, and sibilant and crackling râles were heard over the same area. There was distinct clubbing of the fingers and, to a less extent, of the toes.

The blood showed: hemoglobin, 87 per cent.; red cells, 4,700,000, and leukocytes, 14,000. The differential counts gave polynuclears from 55 to 60 per cent. and mononuclears 32 to 40 per cent. The Wassermann test was negative. The urine showed nothing of note, and the functional test gave 58 per cent. of phthalein excretion in two hours. Repeated sputum examinations did not show tubercle bacilli. The Roentgen-ray report (Dr. Manges) was: "The right upper lobe shows a dense fibrous mass with possibly a cavity or a small amount of lung tissue left."

Progress.—Immediately after admission to the hospital the patient began to improve. The cough became less severe, expectoration lessened, his weight increased (12 pounds in two months) and his strength returned so that he was able to be up during the entire day. He had no elevation of temperature, except for occasional rises to 99 and 100. He was

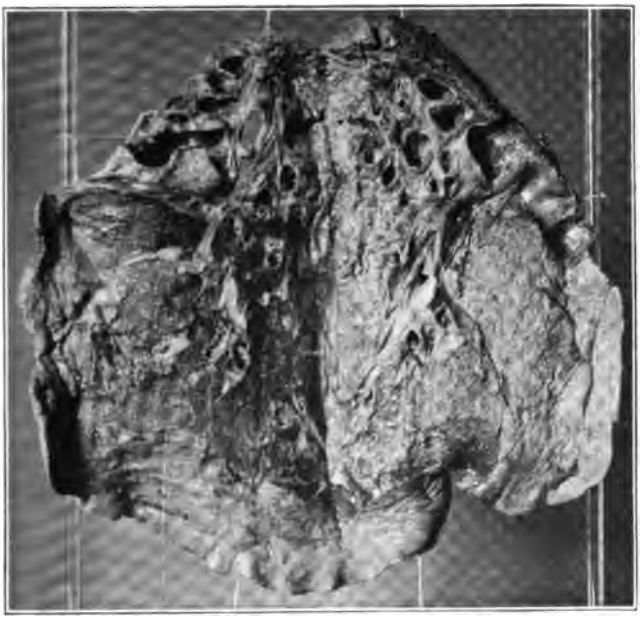

Fig. 1 (Case 1).—Right lung cut open. The sharp line of demarcation between the bronchiectatic upper lobe and the normal lung tissue of the lower lobe is the interlobar fissure. The upper lobe has been converted into a series of cavities as a result of multiple saccular dilatations of the bronchial tubes. Between the dilated bronchi the lung tissue is largely replaced by densely firm fibrous tissue. Very little air-containing pulmonary structure remains. No gross evidence of pulmonary tuberculosis could be found. The lower portions of the lung show passive congestion and slight edema. The opposite lung shows the lobar pneumonia from which the patient died.

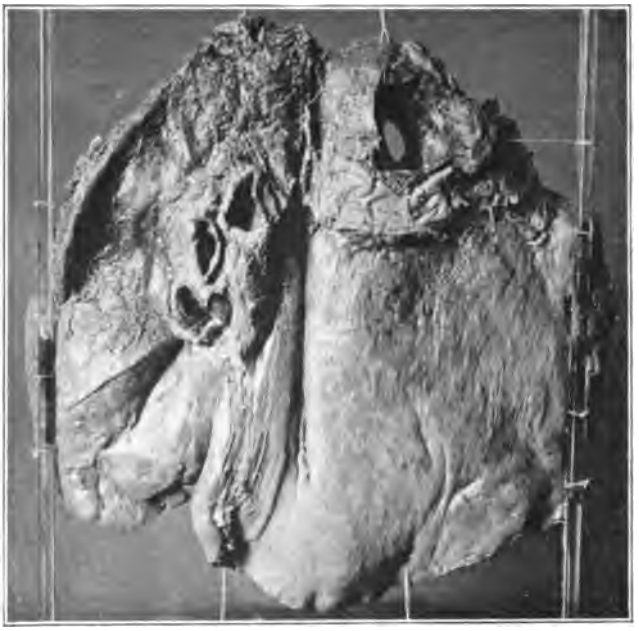

Fig. 2 (Case 1).—External view of same lung as in Figure 1. In the upper portion is seen a trap door of tissue cut in the posterior wall of the largest saccular dilatation exposing to view the interior and the distal wall with the opening of the bronchus therein. The pleura over the upper lobe is thickened and was densely adherent, causing some laceration of the lung tissue during removal. The pleura over the lower lobe is smooth, glistening and apparently normal.

Fig. 3 (Case 2).—Right lung. The upper half of lung shows advanced bronchiectasis. The dilatations are for the most part saccular, although cylindric in some areas, as illustrated on the left side, where the bronchus has been split in its long axis. The bronchial walls are not only dilated, but at points markedly thickened. The lesion corresponds probably to the type described as dilatation with thickening in contradistinction to dilatation with thinning. The intervening tissue is dense and firm, and here and there can be found small fibrocaseous areas, not only throughout the bronchiectatic area, but also in the lower lobes. A small tuberculous cavity can be seen in upper right of specimen at apex. The pleura overlying the upper half of the lung was densely adherent and irregularly thickened.

Fig. 4 (Case 2).—Left lung. The bronchiectasis is of the same character as in the right lung (Fig. 3), though not quite as extensive. Its sharp limitation to the upper portions of the lung is striking. On the right side of specimen where hook is inserted a rather large cavity is seen, the wall of which presents the usual appearance of a tuberculous lesion. In the lower portions of the lung are numerous conglomerate tubercles. The pleura overlying the upper lobes is thickened and at time of necropsy was quite firmly adherent.

Fig. 5 (Case 3).—Left lung. The apex of the upper lobe is converted into a single cavity with a thin, densely firm fibroid wall composed largely of thickened pleura. Microscopic sections of the wall are largely fibrous tissue. The lower portion of the upper lobe and all of the lower lobe are transformed into a series of cavities which intercommunicate in a remarkable fashion. These cavities are bronchial dilatations. The opposite lung showed a lesion of lobar pneumonia at necropsy, and was free from tuberculosis. A discussion as to the character of the large cavity, whether tuberculous or bronchiectatic, or both, is contained in the text.

discharged on request and admitted to a sanatorium during the following summer months, where the diagnosis of *advanced tuberculosis* was made. He was readmitted under our care in the autumn considerably improved, afebrile, but still suffering from a distressing cough and considerable expectoration. The physical examination was identical with that of previous admission. It was our opinion that he suffered with a localized nontuberculous fibrosis of the right upper lobe with perhaps some bronchial dilatation giving rise to signs of cavity. The opposite lung was clear. He was feeling particularly well when an attack of lobar pneumonia with involvement of the left lung supervened from which he died in three days.

Remarks.—The principal reasons for excluding tuberculosis were the apparent freedom from involvement of the left lung in the presence of so well marked a lesion in the right upper lobe and the absence of tubercle bacilli in the sputum. He had been in three sanatoriums; in each the diagnosis of advanced tuberculosis was made. In one sanatorium no examination of the sputum was made.

Necropsy (Dr. Dry. Only the relevant findings are reported in this and subsequent cases).—Lobar pneumonia of left lung. The right pleura was thickened and densely adherent over the upper lobe only. The upper right lobe showed marked fibrous change and cavities throughout due to multiple saccular dilatation of the bronchi. No evidence of tuberculosis.

CASE 2.—*Bronchiectasis involving the upper portions of both lungs, associated with a chronic ulcerative tuberculosis of the same area with small cavities. The bronchiectatic dilatations were in excess of the tuberculous cavities. The impossibility of diagnosing bronchiectasis under these conditions.*

L. S., No. D 5237, man, white, pedler, aged 58, was admitted May 27, 1914, and died Jan. 24, 1916. The past history was negative. He denied having had syphilis.

Present Illness.—Ten years ago he applied to a local hospital for treatment for "bronchial trouble" characterized by a constant annoying cough with expectoration which at times was blood streaked. Since then he had never been entirely free from cough except for very short intervals, usually in the summer months. He had been a patient in various hospitals and sanatoriums with the diagnosis of tuberculosis. At the time of admission to our care his cough was moderately severe and productive, especially at night, of a large amount of yellowish sputum. Blood spitting occurred on numerous occasions, never amounting to more than streaked sputum and rarely lasting more than a day or two. Hoarseness was present at various times. The appetite had been fair, but digestion poor. His best weight was 124 pounds at the time of onset ten years ago, his lowest weight 99 pounds six months ago, and present weight 104 pounds. He had generally lost

strength, although feeling better at times; on admission he was quite weak.

Physical Examination.—He was poorly nourished and pale. The thorax was somewhat rounded and emaciated. The right side was smaller than the left and flattened anteriorly over the upper half. The percussion note was hyperresonant over the entire chest anteriorly except below the right clavicle to the second rib; posteriorly resonance was impaired from the apexes to the spine of the scapulae on both sides and over the right base from the angle of the scapula downward. The breath sounds were generally tubular throughout except below the fourth rib anteriorly, where they were bronchovesicular, and posteriorly below the angles of the scapulae, where they were distant, especially on the right side and corresponding to the area of dulness. The breath sounds on the left side in the upper half were of a typical amphoric quality. Abundant râles of all types were heard throughout the entire pulmonary area, with greatest predominance in the upper lobes, especially on the right side. Vocal fremitus and resonance were quite distinct over the upper chest, especially in the right side and diminished at the right base. The extremities did not show clubbing.

The blood showed: hemoglobin, 70 per cent.; red cells, 4,400,000; leukocytes, 11,000 to 18,000. The polynuclear count varied from 64 to 76 per cent., and the mononuclears from 24 to 36 per cent. The Wassermann test was negative. The urine had a low specific gravity with albumin and hyaline casts. The phthalein output varied from 29 to 40 per cent. in two hours. The sputum contained large numbers of tubercle bacilli.

Temperature Record.—Except for a few months, he was under constant observation from May, 1914, to January, 1916, when he died. For the greater part of this time he was afebrile, except for an occasional week when he would have a slight afternoon rise in temperature for several hours, not exceeding 99 to 100, and, still more rarely, an acute "flare up" to 101 or 102 for several afternoons. The third hour temperature during the last month of life was rarely above normal, and during the last two weeks was subnormal with diurnal oscillations of 2 and 3 degrees. The bedside chart stood in marked contrast with those of fellow patients manifesting the irregular fever so frequently found in advanced tuberculosis.

Progress.—The clinical course was one of progressive weakness until the final month of life, when he was generally confined to bed. The cough was at all times distressing and productive. Blood streaked sputum was frequent and transient in duration. His death, though not unexpected, occurred rather suddenly.

Necropsy (Dr. Dry).—Marked thickened adherent pleura on both sides. Cavities throughout the upper portions of both lungs with marked fibroid changes. The bronchiectatic were in excess of the tuberculous cavities.

CASE 3.—*Extensive bronchiectasis and tuberculosis limited to the left lung. A large cavity in the upper lobe with saccular bronchiectasis of the upper and lower lobes. The question at necropsy as to whether the large apical cavity was tuberculous or bronchiectatic decided only after a careful study by the pathologist. Diagnosis of bronchiectasis suspected during life.*

V. D., No. D 2425, woman, white, mill-worker, aged 20, admitted Nov. 6, 1913, died Feb. 29, 1916. There was a family history of tuberculosis. The previous history was negative.

Present Illness.—The onset was about two years ago with cough and weakness. She was sent to a state sanatorium where she remained for six weeks. She kept house until one year ago when she returned to work in a mill, where she continued until one month ago, when she stopped because of cough and hemorrhages from the lung. The cough of late had become more and more severe and productive of considerable yellowish white sputum which was often blood streaked. The first hemorrhage amounted to a "basinful." She had no pain, but there was dyspnea on exertion. Chilliness and fever were frequent, and night sweats occurred every now and then. Her best weight was 107 pounds three months ago, weight at present 72 pounds.

Physical Examination.—An ill nourished, emaciated, pallid young adult woman. She had moderate dyspnea with slightly cyanotic lips. The chest was flat and emaciated with accentuation of the bony prominences and depressions. The respirations were rapid and shallow with general limitation, especially of the left side. Bronchial fremitus was distinctly felt over the entire left lung. Percussion revealed a slight quality of tympany on the right side anteriorly and posteriorly to the fourth thoracic spine, below which the note was impaired; on the left side dulness extended from the apex to the fourth rib anteriorly, and there was impaired resonance over the entire surface posteriorly, except from the second to the fourth rib, where it approached tympany. Breath sounds were loud and tubular over the entire pulmonary area, especially on the left side, where from the clavicle to the third rib anteriorly and between the second and fourth spine posteriorly, they were distinctly amphoric. Scattered râles of all types were found throughout the lung, especially on the left side. The extremities did not show clubbing.

The blood showed: hemoglobin, 65 to 70 per cent.; red cells, 5,400,000 to 4,300,000; leukocytes, 14,000 to 18,600. The polynuclears varied from 66 to 80 per cent, and mononuclears 18 to 28 per cent. The Wassermann test was negative. The urine was clear. The sputum contained tubercle bacilli.

Progress.—After staying in the hospital under observation for eight months the patient felt slightly better and was transferred to a sanatorium in the country. The cough, expectoration and fever remained unchanged. Hemoptysis was fre-

quent, usually in the form of blood streaked sputum, but on several occasions it was so profuse as to be alarming. The third hour temperature record showed constant afternoon elevations to from 101 to 103 with rapid pulse. After the lapse of one year she returned in about the same condition, but physical examination showed that the left lung was more extensively involved and the right lung considerably improved. We could not account for these changes in the physical signs, except that possibly many of the previous findings in the right lung were due to an associated nontuberculous process which had cleared. We were at a loss to explain the signs of extensive involvement with cavity formation on the left side and so little involvement on the right side. In the ward classes it was pointed out that "perhaps an associated unilateral bronchiectasis" was present. The patient became weaker and had arthritis of the left knee in the last three months of life. The hemoptyses, so frequent on the first admission, were entirely absent. The temperature showed marked diurnal oscillations. Death resulted from lobar pneumonia of the right lung on the second day of its course.

Necropsy (Dr. Dry).—Lobar pneumonia of the right lung, which showed no signs of tuberculosis. The pleura was thickened and adherent over the whole of the left side. The upper lobe of the left lung showed a large cavity with a fibrous wall at the apex and numerous smaller cavities due to bronchiectasis. At necropsy it was not possible to say whether the large cavity was tuberculous or bronchiectatic. The subsequent studies in the pathologic department by Dr. Coplin established its tuberculous nature. Throughout the remainder of the upper lobe and through the lower lobe there was a diffuse, saccular and cylindric bronchiectasis. The lung showed no gross evidence of tuberculosis, although microscopic sections from numerous areas revealed chronic caseous tuberculous bronchitis, fibrocaseous peribronchitis, caseous pneumonia, incomplete atelectasis, and fibrosis. Many of the bronchi showed a deficiency or absence of cartilaginous tissue suggesting faulty bronchogenesis.

CASE 4.—*Well marked acute tuberculosis of recent onset involving both lungs. No signs of cavity formation, yet necropsy revealed a bilateral bronchiectasis of limited extent in both upper lobes.*

E. D., No. F 2055, man, white, farmer, aged 27, was admitted Oct. 21, 1915, and died March 10, 1916. An abscess of the neck (tuberculous glands?) had been opened two years before. There was no history of syphilis.

Present Illness.—The onset was two months before with pain in the throat, hoarseness and cough. These increased in severity; the cough was productive of a considerable quantity of blood streaked sputum. He had lost 42 pounds in weight.

On admission he complained of chilliness, fever and night sweats.

Physical Examination.—He was pale and emaciated. The larynx was red, and cords swollen and extensively ulcerated (tuberculous). The chest was flat and emaciated with limited expansion. The percussion note was generally clear, except above the right clavicle and over the same apex posteriorly, where it was distinctly impaired. The breath sounds were generally harsh with prolonged expiration, most marked in the upper part of the lungs. Distinct cogwheel breathing was audible over the left base posteriorly. Scattered crackling râles were heard over the upper halves of both lungs. The extremities showed beginning clubbing of the fingers and toes.

The blood showed: hemoglobin, 67 per cent.; red cells, 4,700,000, and leukocytes 16,000. The polynuclears were 88 per cent. and mononuclears 12 per cent. The Wassermann test was negative. The urine showed albumin and hyaline casts. The sputum did not contain tubercle bacilli.

Progress.—From the time of admission the course was progressively downward with weakness, irregular fever, night sweats, pain in the throat, hoarseness, shortness of breath and difficulty in swallowing. He died as the result of progressive asthenia.

Necropsy (Dr. Dry).—There was marked pleural thickening over the apexes of both lungs, more marked behind. Both upper lobes showed fibrosis and many dilated bronchi. Throughout both lungs there were many miliary tubercles. There was a tuberculous cavity at the left apex.

CASE 5.—*Bilateral apical bronchiectasis associated with bilateral ulcerative tuberculosis. Adhesive pleuritis with fibrosis of the lungs. The recognition of both conditions during life.*

M. B., No. F. 2060, man, white, aged 30 years, was admitted Oct. 29, 1915, and died May 17, 1916. One brother, at present in good health, was treated for tuberculosis some years ago. The past history was negative.

Present Illness.—The onset occurred two years ago with an attack of pleurisy, since which time he has had a moderately severe cough with expectoration of moderate amounts of mucopurulent sputum, at times blood streaked. He is frequently dyspneic, especially on exertion. He has been losing strength gradually, until at present he is unable to work. His best weight was 120 pounds five years ago, and his present weight is 104.

Physical Examination.—The chest was markedly emaciated and showed a deep depression of the lower sternum and right half. The expansion was generally limited, especially on the right side. The percussion note approached tympany above and below both clavicles. The breath sounds were generally harsh with prolongation of expiration and at both apexes

anteriorly and posteriorly distinctly cavernous in character. There were numerous râles of all types over the entire chest, especially at the apexes. The extremities did not show clubbing.

The blood showed: hemoglobin, 74 per cent.; red cells, 4,510,000, and leukocytes, 13,600; lymphocytes, 22 per cent.; polynuclears, 76 per cent.; eosinophils, 2 per cent. The urine showed a trace of albumin with a few hyaline and granular casts. The sputum was positive for tubercle bacilli. The Wassermann test was negative.

The x-ray (Dr. Borzell) showed extensive bronchiectasis involving both upper lobes with marked fibrosis. On the right side as far down as the seventh rib the pleura was very much thickened. There was considerable infiltration of the right lower lobe.

Progress.—For six months the condition remained unchanged. He was discharged on request and readmitted May 4, suffering from a profuse hemoptysis. The hemorrhage gradually ceased, but he became progressively weaker, and died, May 17. The diagnosis of chronic pulmonary tuberculosis with bilateral cavity formation with associated bronchiectasis was made both by the clinician and the roentgenologist and confirmed by necropsy.

Necropsy (Dr. Dry).—Both pleural cavities were completely obliterated by adhesions, especially dense over the apexes. In the removal of the lungs, the apical adhesions caused a tearing of the pulmonary tissue. The lungs showed extensive fibrosis in the upper lobes with numerous small cavities, which, for the most part, were saccular bronchiectases, and in each upper lobe there was a distinct tuberculous cavity about 3 cm. in diameter.

BRONCHIECTASIS IN RELATION TO SYPHILIS AND TUBERCULOSIS

Syphilis was long considered an important factor in the "pneumopathies" until Laennec showed the unity of the anatomic lesions of tuberculosis. Thereafter tuberculosis assumed the greater importance. Recently Tripier and other French writers have argued on anatomic and clinical grounds that syphilis is the cause of the majority of cases of bronchial dilatation. They exclude those cases due to foreign bodies or stenosis and the group with cylindric dilatation generalized in one or both lungs which is observed in infants and more rarely in young subjects under the influence of repeated attacks of coughing and follow-

ing various lesions causing compensatory dilatation. Abecassis[1] reported thirteen instances of bronchial dilatation associated with other syphilitic lesions such as aortitis, aneurysm, tabes, etc. Garin and Laurent[2] found the Wassermann reaction positive in five cases which they studied. In our five cases the histories were entirely negative, no evidences of syphilis were present, and the Wassermann tests were negative. We have not been able to find in the literature any reference to the finding of the *Spirochaeta pallida* in this type of pulmonary lesion. While syphilis is a possible factor in some cases, most students of the disease are of the opinion that it is not the important factor which the French writers emphasize.

With regard to the relation of tuberculosis to bronchiectasis, we have the extreme views of Rokitansky, who considered the two diseases almost incompatible, and Trojanowsky and King, who found tuberculosis in twenty-one out of sixty-eight, and in twenty-five out of seventy cases, respectively. In our five cases, tuberculous lesions were associated in four instances. King[3] classified seventy cases of bronchiectasis occurring at the Brompton Hospital as follows: (1) "pure bronchiectasis," those associated with tuberculosis, thirty-six cases; (2) "traumatic bronchiectasis," those resulting from aneurysm, tumor, foreign bodies, syphilitic stricture, nine cases; (3) "tubercular bronchiectasis," those associated with tuberculosis, twenty-five cases. Expressed in percentage, nontuberculosis bronchiectasis occurred in 66 per cent. and tuberculous bronchiectasis in 34 per cent. of the seventy cases. With regard to the "tuberculous bronchiectasis," King is of the opinion that all of these cases were primarily tuberculous.

Moderate degrees of bronchial dilatation are not infrequently found associated with pulmonary tuberculosis at necropsy; but clinically the association can

1. Abecassis: Lyon thesis, 1910.
2. Garin and Laurent: Jour. physiol. et path. gén., 1910, xii, 553.
3. King: Scot. Med. and Surg. Jour., 1904, xiv, 42, 481.

be demonstrated only rarely, even when fairly well marked. A probable explanation is found in the fact that when bronchiectatic lesions exist with tuberculosis, they are most frequently found in the upper lobes, and are confused with signs due to tuberculous excavation. A comparison of the clinical and pathologic reports of the Phipps Institute, Philadelphia, is interesting in this connection. Among 3,551 patients with tuberculosis, only 5 were complicated with bronchiectasis; among 320 necropsies, bronchial dilatation was frequently found and distributed throughout the lungs as follows: left upper lobe, 40; right upper lobe, 48; right middle lobe, 31; left lower lobe, 28; right lower lobe, 24. The etiologic relationship of the two lesions is emphasized by the relatively greater frequency of involvement of those portions of the lungs where tuberculosis usually has its initial and most extensive lesion.

In the cases here reported it is important to decide if possible whether there is any clue to the etiology. So far as the histories are concerned, in no case did the disease seem to follow any severe infection. Certain causes seem unlikely to be of importance, especially those which affect the whole of the lung structure. Thus the mechanical pressure of secretion, increased air pressure, atrophy of the bronchial wall, alteration of nutrition, paralysis of the fibers, nervous causes, do not seem likely to operate so locally. But certain other causes may have a definite influence. Among those are pneumonia, tuberculosis, extrabronchial traction, most often caused by pleural adhesions to the thoracic wall and fibroid changes in the lung, a local inflammation of the bronchi, and bronchial stenosis (from a foreign body, pressure of aneurysm or tumor, gumma of a bronchus). In general we must agree with Ewart that there must be some elementary factor common to all varieties, and this is obstruction in some form. Traction on the bronchial wall may arise from a peribronchitis or from a chronic

adhesive pleurisy which extends inward. In either case if the process extends so that there is a connection between the bronchial and chest wall, dilatation may follow.

Certain of these possibilities seem to be definitely excluded in all and others in some of our cases. A foreign body, aneurysm or tumor, gumma or syphilis in any form are ruled out. The possibility of pneumonia is difficult to exclude in any case merely from the history, but changes resulting from pneumonia are more important than the pneumonia itself. Tuberculosis was present in four of our cases. However, what seems most important in this series was the condition of the pleura. In all but one the adhesions were limited to the lobe or lobes with bronchiectasis. This must be regarded as an important etiologic factor. However, it should be said that some regard the fibrosis and pleurisy as secondary phenomena to the bronchiectasis. In any event the frequent association of bronchiectasis and fibrosis is agreed on, and as fibrosis is recognized more frequently, its presence should always suggest careful study of the possibility of bronchiectasis.

CLINICAL FEATURES AND DIAGNOSIS

The features of the marked general cases are usually such that a diagnosis should be made readily enough. The problem is a more difficult one in cases of local bronchiectasis. The history may be of help, especially in any detail which suggests the possibilities of a foreign body having gained entrance to a bronchus, but of particular importance is a history of a chronic cough for a long period with considerable expectoration *without marked constitutional disturbances,* especially if the sputum is fetid. The cough being paroxysmal and often induced by change in position is also suggestive. Too much stress should not be placed on the odor of the sputum; in four of our cases there was no marked fetor of the sputum. This may be due to the

fact that in apical bronchiectasis there is better drainage and consequently not the degree of retention common in basal bronchiectasis. The presence of blood in the sputum is not diagnostic, as it occurs with the same frequency in tuberculosis. It was present in all of our cases. The sputum in a marked case is usually characteristic in its amount and character, but in our cases it was not distinctive except at times in Case 1. Dyspnea is common, especially on exertion, and is most marked in the cases with considerable fibrosis.

The problem of diagnosis of these upper lobe cases of bronchiectasis is largely that of differentiation from tuberculosis. When the two exist together, a diagnosis of bronchiectasis at all and, if made, an exact diagnosis as to how much of the change is due to one and how much to the other is impossible. The nontuberculous cases are often regarded as tuberculosis, an error which can be made only through carelessness. The sputum of a patient with advanced pulmonary lesions due to tuberculosis always contains tubercle bacilli. If this was recognized, we would not miss so many cases of chronic nontuberculous lung conditions and call them tuberculous. It would be interesting to know how many such there are in tuberculosis sanatoriums today, with a diagnosis of advanced pulmonary tuberculosis but no tubercle bacilli in the sputum. The first case here reported is an example (the patient was in several sanatoriums with an invariable diagnosis of tuberculosis). It sounds elementary, but evidently requires emphasis to insist that when symptoms and signs point to advanced pulmonary tuberculosis, and repeated sputum examinations do not show tubercle bacilli, the condition is not tuberculosis.

Another point which may aid in diagnosis is the disproportion between the signs in the lungs and the constitutional symptoms (likely to be present if the condition is tuberculosis). This is not invariable, for many tuberculous patients show the same thing; but when present over a long period, it should suggest

careful study of the possibility of bronchiectasis. This was a striking point in Case 1.

The belief that in the diagnosis between a tuberculous and a bronchiectatic cavity, the apical position of one and the basal position of the other may be considered as almost positive evidence, cannot be accepted. We believe that too much importance has been given to this because bronchiectasis with tuberculosis is perhaps more often apical than basal, and because apical nontuberculous bronchiectasis, either unilateral or bilateral, is probably more common than the usual teaching suggests.

Roentgenographic study, particularly by the stereoscopic method, should be practiced in every case with the hope that in the future this diagnostic aid may be developed. At the present time, however, most students of the disease have the opinion that the Roentgen ray is of comparatively little value in the diagnosis of bronchiectasis. In the demonstration of foreign bodies, aneurysm, etc., it has a distinct field of usefulness.

Treatment is largely palliative. The adoption of a semierect or erect posture facilitates drainage in the apical cases. After intratracheal injections the patient should be placed in a recumbent posture. Autogenous vaccines may be tried, although their value is undetermined. The general measures are those usually applied to improve the nutrition of the patient.

SUMMARY

1. In five cases of apical bronchiectasis, the distribution was: right upper lobe, one; right upper and lower lobe, one; both upper lobes, three.

2. Tuberculosis was associated in four cases, three of which were bilateral.

3. Syphilis was apparently excluded as an etiologic factor.

4. Pleural thickening over the site of the bronchiectasis was extreme in all and limited to the area of

bronchiectasis in four. This suggests an important etiologic influence.

5. There was marked evidence of pulmonary fibrosis in the bronchiectatic areas.

6. The diagnosis is difficult, but possible more frequently if looked for in the presence of fibrosis or tuberculosis with which it is not uncommonly associated. Advanced apical bronchiectasis unassociated with tuberculosis may be mistaken for tuberculosis, which error can be avoided by careful sputum examination.

7. The absence of fetid sputum in these cases was probably due to the fact that drainage is more thorough in upper lobe cases.

ABSTRACT OF DISCUSSION

DR. FREDERICK T. LORD, Boston: As regards the pathology, bronchiectasis is a striking feature at necropsy and the impressive picture it presents may lead us to consider it of primary importance, but we should think of it, as close examination of the lungs almost invariably shows, as a relatively insignificant part of a more or less extensive broncho-pulmonary involvement. Concerning the diagnosis: It is at times very difficult to distinguish between bronchiectasis and chronic abscess, and it must be acknowledged that we cannot always make this differentiation. In the presence of such extensive broncho-pulmonary lesions as we have seen illustrated in the photographs shown, this is of less importance than in other clinical cases in which the lesions are of limited extent, as indicated by physical signs and Roentgen examination. In such cases a decision between broncho-pulmonary infection leading to bronchiectasis and chronic pulmonary abscess may be the deciding factor between non-operative and operative treatment. The presence in the sputum of elastic tissue with alveolar arrangement indicates involvement of the lung tissue and a loss of pulmonary substance but does not exclude a complicating bronchiectasis. When the differential diagnosis cannot be established it seems best in the presence of limited and circumscribed involvement to give the patient the benefit of the doubt and consider operative interference.

SPLENECTOMY IN PERNICIOUS ANEMIA

STUDIES ON BONE MARROW STIMULATION *

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In the study of diseases of the blood and particularly of the effects of therapeutic procedures in such diseases it is necessary that one should be able to estimate by reliable criteria any alteration of the relative rate and degree of destruction and regeneration, at least of the formed constituents of the blood, the erythrocytes, leukocytes and platelets. Such information is particularly desirable in pernicious anemia, in which the spontaneous course of the disease is so bizarre. Marked improvement, usually called a remission, occurs frequently in the course of the disease and may easily be attributed to any incidental therapeutics.

The methods for studying the processes of blood destruction and regeneration are few. The enumeration of the formed elements may or may not be of value. It is evident that a given number of a blood element merely represents the balance of destruction and formation. The red cell destruction can be studied by the excretion of urobilin, and perhaps in certain instances by estimating the bile pigments in the blood.[1] Sellards and Minot [2] have pointed out that the study of the tolerance to injections of hemoglobin in man may perhaps furnish valuable information concerning erythrocytic destruction. The presence in the

* From the Medical Service of the Massachusetts General Hospital.
1. Blankenhorn: Tr. Assn. Am. Phys., 1916.
2. Sellards and Minot: Jour. Med. Research, 1916, xxxiv, 469.

peripheral blood of the "bodies" described by Rous and Robertson [3] may also throw light on this subject.

The white corpuscle destruction in certain instances may perhaps be studied by the estimation of certain nitrogenous products in the urine.

There are no known methods for studying the destruction of the blood platelets, since we do not know their ultimate fate. We merely know that their life is short, being from three to six days.

The rate and degree of formation of the formed blood elements can be studied clinically in a number of ways. The chief source of these elements is the bone marrow. Thus, in order to gage the power of regeneration and formation of the formed elements, one must study the activity of the marrow. One must scrutinize, not only the increases of bone marrow activity, but also the intensity and quality of that activity and its possible relation to the therapeutic procedure.

Evidence of increased activity on the part of the marrow in the production of red cells may be shown by an increase of young forms of red corpuscles. The presence of increased numbers of reticulated red cells, especially of a certain type, the presence of blasts, Howell-Jolly bodies, polychromatophilia and certain types of stippling should be considered in studying the activity of the bone marrow. Variations of size and shape of the red cells may be of significance in certain cases.

The decreased activity in the production of red cells may be evidenced by an absence of the factors indicating activity. A rising red count does not necessarily mean an increased activity of the marrow, for the count may rise as the result of a lessened destruction. Increased activity is entirely consistent with an anemia when formation does not compensate destruction. Likewise, an extreme grade of anemia may be associated with decreased destruction and caused by decreased formation.

3. Rous and Robertson: Tr. Assn. Am. Phys., 1916.

Evidence of the activity of the marrow in the production of white cells may be seen in the polynuclear count and perhaps in certain changes in the Arneth formula. A diminished activity is associated with a low polynuclear count and a resulting relative lymphocytic increase. In some instances with diminished activity of the bone marrow the liver and finally other structures may revert to a fetal condition, and white cells resembling fetal cells may be found in the blood stream, especially in cases of tumors involving marrow.

Könnecke,[4] by injections of nucleinate, and von Decastello and Krjukoff,[5] by injections of gelatin, have suggested that the degree of polynuclear leukocytosis caused by these substances furnishes an indication of the functionating ability of the marrow. From our study of this procedure we feel we gain some information concerning the functionating ability of the marrow in regard to its ability to form and send into the circulating blood leukocytes, but not necessarily information concerning the functionating ability of the marrow as a whole.

Increase of the blood platelets in the peripheral blood is also indicative of an increased activity on the part of the marrow supplying the blood platelets. The size, shape and character of these elements is probably also important in determining the activity of the marrow.

When the marrow is functionating above or below normal the three main elements are not necessarily equally affected. The effect may be entirely or predominatingly on one or two of these elements. It is thus necessary in studying the degree of bone marrow activity to consider not only one but all the factors involved.

We have followed our cases of blood disease in their spontaneous course and after treatment especially from the point of view of the degree of bone marrow activity.

4. Könnecke: Deutsch. Arch. f. klin. Med., 1914, cxv, 177.
5. Von Decastello and Krjukoff: Med. Klin., 1911, vii, 225, 267.

Our, as well as other, previous studies have shown that while the amount of destruction of red corpuscles in pernicious anemia is somewhat reduced as a rule after splenectomy, yet this reduction occasionally occurs without therapy. The spontaneous course of the disease is so irregular and variable that it cannot be denied that it is possible to parallel the reduction of the destruction of the red cells after splenectomy with similar reductions without any treatment. Yet it seems probable that the destructive agents are modified to some extent after splenectomy. It is certain, however, that the destructive processes involving the red cells are still present.

Our fifteen cases of pernicious anemia subjected to splenectomy, in accord with other reported cases, show that the important features of the disease, namely, the typical blood picture and relapses with marked destruction, still persist. As von Decastello[6] and others have pointed out, it is possible to attribute improvement to an increase in blood formation as well as to a decrease in blood destruction. We have, therefore, submitted our cases of pernicious anemia to a critical study of the effect of splenectomy on the blood-forming organs with a view of determining if possible the value of this procedure in altering the activity of the bone marrow.

Fifteen cases,[7] which include all of the patients with pernicous anemia operated on by splenectomy at the Massachusetts General Hospital, were studied (from November, 1914, to May, 1916). Ten of these patients were operated on by one of us (Vincent). The other five were operated on by Dr. C. A. Porter, to whom we are indebted for the privilege of including the operative findings of his cases.

One patient with a red count below 1,000,000 died the day after operation, presumably of postoperative shock. There were no other immediate postoperative

6. Von Decastello: Deutsch. med. Wchnschr., 1914, xl, 639, 692.
7. Lee, Vincent and Robertson: THE JOURNAL A. M. A., July 17, 1915, p. 216, reported five of these cases.

deaths, thus giving an immediate operative mortality of 6.6 per cent. The low immediate mortality indicates that with the proper selection of the time of operation in the course of the disease any considerable operative mortality is not to be expected.

Of the fourteen patients who survived, the operation in one case was too recent to afford any data. Of the remaining thirteen patients, one, operated on two and a half months ago, remains in the hospital on account of thrombosis. The other twelve left the hospital three to six weeks after operation, at which time the large majority presented no great change in their blood counts, and they all felt better, looked better, and were less yellow. In all of them the blood picture was that of pernicious anemia. Four patients showed considerable immediate and progressive improvement in the red counts and hemoglobin. Two of the four were transfused, one two days before, the other two days after operation. None of the other patients were transfused within ten days of operation.

The condition of these thirteen patients was ascertained as far as possible two months after operation. Three could not be said to have changed materially, particularly in their blood counts. One case showed a slight increase and one a moderate increase in the red cells. Eight showed a marked increase in the count of red cells. The red counts of these eight cases averaged approximately 4,000,000, with a corresponding improvement in their clinical condition. Nevertheless the diagnosis of pernicious anemia could be made from the blood films.

Of the thirteen patients, there were ten in whom six months had elapsed since operation. At the end of six months five of these ten patients had a relapse. Four of these five at the two months' period had presented very marked improvement. The fifth patient never showed any great improvement.

At the end of a year after operation we had received no information concerning two patients. These two

patients had no relapse within six months. Two patients still alive had not yet gone a year after splenectomy. The patient who presented no improvement at the end of the second month period and was relapsing at the sixth month period was dead within a year after operation. Of five remaining patients, only one had certainly gone a year without a relapse. This patient, however, suffered a typical relapse and died sixteen months after splenectomy. One of the remaining four died sixteen months after operation in his second relapse. Another after sixteen months is now having a very serious relapse after several minor relapses. Still another is having his second serious relapse at the end of the year period. The last patient to be accounted for at the end of the year period had a relapse at six months. He was markedly improved by transfusion, and now has 3,000,000 red corpuscles.

The end results of splenectomy certainly fail to show any permanent results from this procedure.

The eventual progress of the disease is not changed. Nevertheless, it is striking that there was in eight out of thirteen cases a considerable temporary improvement in two months, which persisted in some cases to six months. This improvement was marked though not necessarily more marked than the improvement often seen occurring spontaneously; but it seemed to occur rather uniformly after this procedure.

The formed blood elements derived from the bone marrow have been followed in these fifteen cases. Observations on these elements are presented below.

Leukocytes.—Immediately after splenectomy, as has been the usual experience of others, we observed a leukocytosis, varying from 10,000 to 35,000, with increased polymorphonuclear percentage. This occurred within twenty-four hours after splenectomy and subsided within a few days. As pointed out by Cabot,[8] the white count varies with the progress of

8. Cabot: Modern Medicine, Osler and McCrae, 1913.

the disease, being higher when the number of red cells is higher. We found, as have others, that persistently after splenectomy there was a distinct tendency to a higher level of the white count than occurred in the usual course of pernicious anemia, in which there is usually a leukopenia with often an absolute diminution of polynuclear leukocytes. This increase was both lymphocytic and polymorphonuclear. Perhaps more often there is a relatively greater polymorphonuclear than lymphocytic increase. The polymorphonuclear cells, when increased, tended to give a normal Arneth picture, as contrasted to the abnormal right handed shift which is the usual picture in the spontaneous course of this disease, as pointed out by Briggs.[9] Occasionally a slight eosinophilia occurred.

In general, the leukocytosis immediately after splenectomy and the level of leukocytosis for some weeks afterward contrasted with the average before operation gave a rough index of the future reaction in the red cell forming part of the bone marrow. The patients with the highest leukocytosis tended to show the greatest improvement after splenectomy. Per contra, the patients who showed only a slight increase after splenectomy eventually showed little improvement after this procedure. Such figures do not definitely prove this, but they strongly suggest that a persistently very low polymorphonuclear count in this disease is of value as one of the indicators of bone marrow exhaustion. Under such conditions little improvement is to be expected from any therapeutic measures directed at increasing the activity of the bone marrow.

Platelets.—The number of platelets in pernicious anemia is usually low. Like the leukocyte count, the number of platelets tends in general to follow the curve of the red cells in the usual course of the disease. The platelets show a definite increase three to seven

9. Briggs: Am. Jour. Med. Sc., 1914, cxlviii, 413.

days after splenectomy. This increase usually takes the platelets not only above the average count in pernicious anemia, but often well above the normal, in one of our cases even to 900,000. This increase is usually persistent, though fluctuations occur. Besides the increase in platelets, there are changes in their morphology. A tendency to abnormally large platelets occurs in pernicious anemia. After splenectomy the presence of a considerable number of very large platelets is striking. There also seems to be an abnormal variation in shape. Like the increase in the white count, the platelet increase seems to be of some value as an indicator of the ultimate reaction of the bone marrow in forming red cells. Likewise, a persistently low platelet count in pernicious anemia seems to be one of the criteria of bone marrow exhaustion.

In this connection we have been impressed by the association of the increase of platelets and thrombosis. Thrombosis is not an uncommon complication of splenectomy. It has been reported as a postoperative cause of death. Of course the platelets are not the sole factor in thrombosis. The immediate and directly exciting cause may be infection or some unknown agent. We have noted thrombosis or phlebitis in three of our cases.

In one case it was noted on the fifth day after operation and involved many veins. In the second case it was noted after three weeks. In the third case it was first observed when the patient reported at nine months. In a case of splenectomy in pernicious anemia of Dr. W. S. Thayer, studied by one of us,[10] thrombosis was noted on the ninth day. In this case extensive thrombosis was the cause of death. In our second case of thrombosis a severe gastro-intestinal disturbance was present on the tenth day, although the phlebitis was not evident until the twenty-first day. All of these cases had at the time of the phlebitis a very

10. Minot, Denny and Davis: Arch. Int. Med., 1916, xvii, 101.

large increase of platelets. The majority of our other patients had some days after operation, at the time of marked increase of the blood platelets, vague gastro-intestinal symptoms of varying severity. These symptoms were unlike any that they had had before operation and furthermore were quite different from the gastro-intestinal symptoms, so common after any abdominal operation. The association of this condition with thrombosis or phlebitis of some of the mesenteric veins is possible. This association is of course not proved. It may not be amiss to point out that thrombosis in the usual course of pernicious anemia is extremely rare, but apparently is not uncommon after splenectomy. We are inclined to believe that the thrombosis is in some way related to the marked increase of platelets.

Howell-Jolly Bodies.—There occur in the red cells, particularly after splenectomy, and in other conditions often associated with grave anemia, certain round bodies known as Howell-Jolly bodies. The nature of these bodies is not clearly understood, although they are fairly generally assumed to be nuclear fragments. We were able to find a very few of these bodies in three of our cases before operation. It is probable that these Howell-Jolly bodies could have been found in the other cases if the blood had been subjected to a similar prolonged search. They occurred constantly in every case after operation. These bodies usually appeared in small numbers the day after splenectomy, and gradually increased. In some instances 25 per cent. of the red cells contained them. The usual percentage was from 2 to 10. Their percentage fluctuated, but they were always present in fair numbers as long as we made observations. Their morphology varied considerably; there occurred differences in regard to size, situation in the red cells, multiplicity, and their association to reticulated and polychromatophilic cells. We are unable at present to correlate positively variations in number or type with the clinical progress of the

disease. We are inclined to agree with the general belief that in some way these bodies are related to an increase of bone marrow activity or irritation, or possibly to some change of threshold of output of red cells.

Blasts.—Ten of the eleven cases on which we have adequate data presented within a few days after operation, like other reported cases, a shower of blasts of varying degree. The maximum number of blasts seemed to occur approximately two to ten days after operation. The duration of the blast crisis varied widely and in a few cases persisted for some weeks. The intensity of the reaction in blasts could not be anticipated by the preoperative number of blasts in the blood. The blood of one patient who presented a large number of blasts after operation showed a very rare blast on repeated examinations over a long period of time before operation. It has been our experience that a shower of blasts often precedes a spontaneous remission. This remission may be quite transitory and slight. However, a shower may be seen just before death. After operation a shower of blasts, especially when persistent, seemed to be associated with an ultimate improvement. The findings were not constant and we do not feel that the presence of blasts even in considerable numbers at any stage of the disease including after splenectomy is of much significance as to the future course of the disease.

Reticulated Red Cells.—The percentage of reticulated red cells may perhaps be taken as a measure of the hemopoietic activity of the bone marrow. Normally, about 0.8 per cent. of the red cells are reticulated. In the spontaneous course of pernicious anemia one sees wide fluctuations in the percentage of these cells containing a "reticulum" vitally stained with brilliant cresyl blue. This percentage varied in our cases, from 0 to 20. A high percentage of reticulated cells probably indicates an increased activity of the part of

the bone marrow that produces red cells. This increased activity of the bone marrow is not necessarily accompanied by either a rise in the count of the red corpuscles or in clinical improvement, since this may or may not be counterbalanced by an increased destruction. Likewise, in the event of decreased activity of the bone marrow, an associated decrease in the blood destruction may leave the number of the red cells and the clinical picture unchanged. In order to form any estimation of the bone marrow activity, as indicated by the reticulated cells, it is necessary to make continuous observations over periods of time. Occasional observations are of no value, as they may indicate only transitory tendencies. However, our data show that curves plotted from frequent observations are reliable indicators of bone marrow activity and are the forerunners of increased red cell counts and of clinical improvement in the absence of excessive blood destruction.

Some studies, as yet incomplete, of the character of the reticulated cells, not only in pernicious anemia, but also in other conditions, strongly suggest that the character of these cells is at least as important as the percentage in determining the intensity and permanency of the bone marrow activity. We consider of particular importance the presence of heavy, knotted reticulum, usually in the center of the cell. Such a reticulated cell is found in fairly large numbers under the recognized conditions of very active blood regeneration, as we have seen persistently in hemolytic jaundice and temporarily after direct hemorrhage in normal persons.

Other characteristics of these reticulated cells that seem to us of probable significance are the size of the reticulated cell, the hemoglobin content, the amount, quality, granulation, and distribution of the reticulum. Also of doubtful significance in regard to bone marrow activity is the presence, which we have noted in a few cases, of the hemoglobin-free reticulated cells or

bodies, resembling those described by Rous and Robertson, which they consider as probably red cells in the stage of destruction. We are inclined to believe that when the red cells contain a few scattered, short strands of reticulum, particularly when arranged in the periphery of the cell, the actual percentage of reticulated cells is of slight significance.

In general, two to five days after splenectomy in pernicious anemia we found a slight temporary rise in the reticulated cells. These findings coincide with the blood findings at the time of discharge from the hospital about three weeks later. At that time the red count was usually not much increased, but in the event of a persistent increase of the reticulated cells we found marked clinical improvement associated with an increased red count. This was particularly marked in the two patients on whom blood transfusion was performed at the time of operation. In these patients this rise persisted and reached in eight to twelve days a level of about 15 per cent. of reticulated cells, chiefly of the knotted centrally-placed type. In the event of a short and slight temporary rise in the reticulated cells, if an increase in the red count developed later, there first appeared a second and this time a considerable rise in the reticulated red cells. This rise was usually evident about three weeks after splenectomy and was often associated with a shower of blasts. With the appearance of a definite remission, when the red cells approached normal, the reticulated red cells fell to normal figures or lower, with the removal of the necessity of abnormal bone marrow activity.

The degree of the response varied. Those cases in which increases of reticulated cells had been observed either in the spontaneous course of the disease or after transfusion usually showed greater increases after splenectomy. However, we were able to observe increases in reticulated red cells after splenectomy in two cases in which no essential increase in reticulated red cells had previously been noted, either

in the spontaneous course or after transfusion. These increases tended to be relatively slight, since in such instances it is probably safe to assume that we are dealing with an exhausted bone marrow, apparently incapable of reacting to anything except the strongest stimulation, that is, the changes, whatever they may be, that take place after splenectomy. Two patients in severe relapse after splenectomy have shown a truly remarkable blood picture of bone marrow reaction following transfusion. This was not seen in three others.

The increased reacting power of the bone marrow under the influence of transfusion in the first two cases seems to be related in some way to the absence of the spleen.

The further study of the blood films stained by Wright's stain showed only the characteristics that have been noted previously by us and others. Our observations on polychromatophilia, anisocytosis and stippling have furnished little additional evidence as to the functionating ability of the bone marrow.

While the presence of blasts and of Howell-Jolly bodies is in some way related to the activity or change in threshold output of the bone marrow, we are unable to correlate definitely our data concerning them and those of the reticulated red cells. The reticulated cells furnish the most reliable data concerning the activity of the erythrocytic elements of the bone marrow. The increase in the platelets and the polynuclear leukocytes after splenectomy in pernicious anemia furnishes further evidence of the effect of this procedure in stimulating the bone marrow of these cases.

It is to be noted that splenectomy in pernicious anemia has in nowise a specific stimulating effect on any one portion or on any one function of the bone marrow. It apparently acts grossly on all portions, though the effects are seen at different periods of time in relation to the operation. We attribute the temporary improvement in pernicious anemia after splenectomy to two factors: first, an associated diminution

in the blood destruction; and second, the associated increase in activity of the bone marrow. We do not attempt to explain the precise mechanism by which splenectomy brings about an increased activity of the marrow. Certain stimulating effects after splenectomy are seen almost immediately, as in the case of the increase in the polymorphonuclear leukocytes. The increase in the platelets tends to occur somewhat later, and the main increase of the reticulated cells, when it occurs, seems to be inaugurated still later. This effect on the part of the bone marrow which forms red cells is much more difficult to bring about and also is slower.

While in general one assumes that the changes in activity of the bone marrow is induced by some unknown irritating or stimulating process, it is possible to explain certain features on other grounds. It may be that, as Naegeli[11] has suggested, we have the threshold of output changed so that cells normally present in the bone marrow but not in the blood may appear in the peripheral circulation. Perhaps the spleen normally may have some inhibitory effect on the bone marrow. On the latter basis it is hard to explain the considerable leukocytosis, similar to that occurring in certain infections, the increase of platelets, and the occurrence at necropsy in pernicious anemia of a red bone marrow. In favor of this assumption one may point to the appearance of Howell-Jolly bodies and certain other characteristics of the red cells that cannot be positively related to such characteristics of the red cells as reticulation, which are generally assumed to indicate, not only the earlier appearance of these cells, but also an actual increase in the formation. It seems probable that both these considerations play a part in the changed picture. We use the term stimulation of the bone marrow in the general sense of indicating the inauguration of the changes.

11. Naegeli: Blutkrankheiten und Blutdiagnostik, Leipzig, 1912.

By the use of these methods we conclude that one finds stimulation of the bone marrow in pernicious anemia frequently occurring spontaneously. One may find stimulation of the bone marrow usually associated with improvement after transfusion and after splenectomy. Splenectomy seems to result in the greatest stimulation of the bone marrow of any known therapeutic measure. It acts on the whole bone marrow and not only on the portion that forms red cells. However, splenectomy does not alter the essential course of the disease. While more constant stimulating effects are seen after splenectomy, yet we can roughly parallel any individual case of bone marrow stimulation after splenectomy with a case of bone marrow stimulation that occurred either spontaneously or after transfusion.

It is evident that from splenectomy one can attain stimulation but once. Transfusion, while perhaps of less constant and of less active effect, has two great advantages. It is relatively simple and can be repeated a number of times. Transfusion does not modify the destructive agencies at work in pernicious anemia. These considerations must be carefully weighed in advising any therapeutic procedures in this disease.

LATE RESULTS OF SPLENECTOMY IN PERNICIOUS ANEMIA

A STATISTICAL AND CRITICAL REVIEW *

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The striking improvement that has been shown to follow removal of the spleen in such diseases as hemolytic jaundice and Banti's disease has naturally led to an extension of this clinical procedure to allied conditions. In 1913 three investigators, Eppinger,[1] Decastello[2] and Klemperer,[3] working independently, applied splenectomy to the relatively common and grave disease, pernicious anemia. It is interesting that Eppinger was led to adopt this procedure by observing after splenectomy a diminished output of urobilin and other evidences of decreased hemolysis. Decastello, on the other hand, had noted the improvement that followed splenectomy in the related conditions, hemolytic jaundice and Banti's disease; whereas Klemperer was influenced by the clinical observation that splenectomy for such conditions as rupture of the spleen was in some instances eventually followed by polycythemia.

Such marked improvement was noted in these earlier cases that the procedure was quickly and widely repeated, chiefly in Germany and in this country, so that a fairly large group has already become available for study. More prolonged observation, however, has showed that besides a considerable mortality from the

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1. Eppinger, H.: Berl. klin. Wchnschr., 1913, xxix, 2409.
2. Decastello, A. von: Deutsch. med. Wchnschr., 1914, xl, 639; later reports by personal communication to the author.
3. Klemperer, G., and Hirschfeld, H.: Therap. d. Gegenw., 1913, liv, 385.

operation and postoperative complications, very few of the patients continue steadily to improve; in almost all the characteristic blood picture of pernicious anemia remained, and not a few died from relapses of the disease in the first year or two after operation. The object of this paper is to ascertain as far as possible by a correlation of the published reports, with later results obtained by personal communication, just how valuable splenectomy has thus far proved to be in pernicious anemia.

Although it has been impossible to get additional reports from some of the German authors, and of some patients who have been lost sight of, nevertheless the results obtained in the last two and one half years are sufficiently concordant to give evidence of some value. In drawing conclusions from any such review, however, it must be remembered that certain difficulties are unavoidable. For instance, the dividing line between pernicious anemia and some of the other primary blood diseases is necessarily such a shadowy one that the possibility of an incorrect diagnosis must always be borne in mind. Then, too, the concept of pernicious anemia varies so much with different authorities that cases included as such by one author might easily be rejected by another. Thus one of the earlier cases of splenectomy that was followed by marked and long-continued improvement, when subjected to critical analysis, seems to the writer rather a case of acquired hemolytic jaundice than of true pernicious anemia. In another case reported as pernicious anemia, the diagnosis was later changed to hemolytic jaundice on account of the subsequent appearance of acholuric jaundice with diminished resistance of the erythrocytes. As such variations in diagnosis are apt to include less serious diseases under the head of pernicious anemia, or diseases in which splenectomy is already known to be of benefit, the present statistics will be correspondingly favored by such inclusions. In applying the present figures to

prognosis, however, it is fair to offset the inclusion of such cases with the results that must inevitably follow the better selection of cases and better preparation for operation. A third consideration is that the term pernicious anemia may later be found to include more than one clinical entity. (Compare the great variations that occur in the size of the spleen, in the bone marrow reactions, in the evidences of hemolysis, and in the duration of the disease.) If this were found to be true, it might well be that some of the apparently discordant results that have been observed after splenectomy are due to the fact that the operation was of value in one or more types and contraindicated in the others. The results of these studies are included in Table 1.

ANALYSIS OF RESULTS

From Table 1 it will be seen that of the 153 individuals whose spleens were removed, thirty died within six weeks, presumably from the effects of the operation, a mortality of 19.6 per cent. Of the remaining 123 patients, all but twenty-four showed a distinct improvement, both in general condition and in blood picture. Of the twenty-four individuals that survived the operation but failed to improve, a few were obviously harmed by it. To this group belongs Pappenheim's case, splenectomized at a favorable time, when the patient was entering a remission. The condition, nevertheless, was aggravated by the operation, the blood showed signs of increased destruction and a serious relapse began. The improvement noted in the majority of cases lasted varying periods. Thus at the end of six months, of fifty-three patients who had survived operation for more than six weeks and were still under observation, forty-four had still continued to improve and none had died, but nine had already relapsed.

At the end of the first year after operation, there remained twenty-seven patients who were still under observation. Of these, Decastello's series is the most

TABLE 1.—RESULTS OF SPLENECTOMY IN PERNICIOUS ANEMIA

Observers	References	Number of Cases	Postoperative Results			Total Deaths
			Deaths	No Improvement	Improved	
Decastello, A. von..	Deutsch. med. Wchnschr, 1914, xl, 639	13	4	1	8	7
Eppinger, H.	Berl. klin. Wchnschr., 1913, xxix, 2409	7	0	0	7	?
Fahreus, M. B.	Svensk. Läk. Förhand., 1915, viii, 249	3	1	0	2	2
Fenckel	Verhandl. d. deutsch. Gesellsch. f. Chir., 1914, xliii, 233	2	0	2	0	1
Flörcken	Verhandl. d. deutsch. Gesellsch. f. Chir., 1914, xliii, 231	2	1	0	1	1
Frangenheim	Sitz. d. allg. Aerzt. Ver. z. Köln, München. med. Wchnschr., 1914, lxi, 1760	2	1	1	0	1
Giffin, H. Z.	Personal communication to the author	31	3	6	22	7
Guleke	Verhandl. d. deutsch. Gesellsch. f. Chir., 1914, xliii, 227	2	2	0	0	2
Hansing, W.	Med. Klin., 1914, x, 1544	2	2	0	0	2
Hossli, H.	Cor.-Bl. f. schweiz. Aerzte, 1914, xliv, 1171	2	1	0	1	1
Klemperer, G.	Therap. d. Gegenw., 1913, liv, 385	14	4	2	8	5
Lee, R.	THE JOURNAL A. M. A., July 17, 1915, p. 216; personal communication to the author	15	1	4	10	3
Longcope, W. T.	Personal communication to the author	2	1	1	0	1
Percy, N. W.	Surg., Gynec. and Obst., 1915, xxi, 360; personal communication to the author	19	2	2	15	4
Roblee, W. W.	THE JOURNAL A. M. A., March 6, 1915, p. 796; personal communication to the author	2	0	0	2	1
Roemer	Berl. klin. Wchnschr., 1914, li, 669	2	0	0	2	1
Thayer, W. S.	Tr. Assn. Am. Phys., 1914, xxix, 489; personal communication to the author	2	0	0	2	1
Vogel, C.	Personal communication to the author	7	3	1	3	4
Jagic, N. von.	Wien. klin. Wchnschr., 1914, xxvii, 1536	3	0	0	3	0
Single cases[4]		21	4	4	13	9
Total		153	30	24	99	53

4. The single cases were reported by various authors as follows:
Anschutz: Verhandl. d. deutsch. Gesellsch. f. Chir., 1914, xliii, 232.
Baldwin, J. F.: Med. Rec., New York, 1915, lxxxvii, 230.
Brill, N. E.: Tr. Assn. Am. Phys., 1915, xxx, 547.
Buerger, L., and Ottenberg, R.: Med. Rec., New York, 1914, lxxxvi, 860; later report by personal communication to the author.
Coleman, W.: Tr. Assn. Am. Phys., 1914, xxix, 470.
Dahl, R.: Hygiea, 1914, lxxvi, 471; later report by personal communication to the author.
Harpole, W. S.: Surg., Gynec. and Obst., 1914, xviii, 243; later report by personal communication to the author.
Huber, O.: Berl. klin. Wchnschr., 1913, L, 2179; later report by personal communication to the author.
Judell: Personal communication from Dr. Moffitt to the author.
Mann, A. T.: Journal-Lancet, 1915, xxxv, 294.
Moffitt, H. C.: Am. Jour. Med. Sc., 1914, cxlviii, 817.
Mosse, M.: Berl. klin. Wchnschr., 1913, L, 2088.
Muhsam, R.: Deutsch. med. Wchnschr., 1914, xl, 380.
Pappenheim, A.: Deutsch. med. Wchnschr., 1914, xl, 412.
Penrose, C. A.: South. Med. Jour., 1915, viii, 879.
Pepper, O. H. P., and Austin, J. H.: Arch. Int. Med., July, 1916, p. 131.
Port, F.: Berl. klin. Wchnschr., 1914, li, 546.
Rodman, J. S.: Personal communication to the author.
Stewart, F. T.: Personal communication to author.
Talley, J. E., and Jopson, J. H.: Personal communication to the author.
Turk, W.: Deutsch. med. Wchnschr., 1914, xl, 371.

important, not only because he and Eppinger were the first to try this procedure and therefore the cases could be followed for a longer time, but because the early successful results have been greatly modified by time. Of six patients at the time of his publication several months after operation, four showed such great improvement that except for the microscopic appearance of the blood they might have almost been considered cured. Two years later, however, two were dead and one was in as poor condition as before operation. Of the other two important early series, Eppinger's and Klemperer's, it has proved impossible to get additional information. The figures for the whole group of twenty-seven cases, however, show that the initial improvement has been maintained in less than half of the cases.

TABLE 2.—LATE RESULTS AFTER SPLENECTOMY IN PERNICIOUS ANEMIA

	After One Year	After Two Years
Number cases known	27	6
Still improved	11	3
Relapsed	7	2
Died subsequently	9	1

A small but interesting group is formed by six individuals that have been known to have lived two years or more after operation (Decastello 2, Giffin, Harpole, Huber, Thayer). Of these, Giffin's patient had had the disease for two and a half years; the anemia was not extreme at the time of the operation, and the spleen was much enlarged (1,640 gm.). Improved by the operation, he died three years later from pneumonia. In Decastello's two cases the disease had existed for less than a year, the anemia was severe, and the spleen but slightly increased in size. Both patients improved after operation both clinically and as to the blood picture; but whereas one in a subsequent report was in poor condition, the other was without symptoms, although the blood picture was

still that of pernicious anemia. Harpole's patient was known to have had pernicious anemia for two years, and at the time of operation the anemia was moderately severe and the spleen twice the normal size. After splenectomy there occurred immediately an active bone marrow reaction with marked clinical improvement. The patient has continued in fair health, with only a slight anemia, but with persistence of spinal cord symptoms. Huber's patient, who was considered moribund at the time of operation, improved rapidly for seven weeks, relapsed, and later underwent a spontaneous remission. After two and a half years, she was still in good condition and able to do her housework, but still anemic. Thayer's patient, having had the disease one year, improved after splenectomy, although there was no bone marrow reaction. After eighteen months the patient relapsed to the same condition as before operation and was last reported in poor condition.

Estimation of the value of such a procedure as splenectomy in pernicious anemia must take into consideration not only the actual results obtained, but a comparison, as far as is possible, with the probable results if operation had not been undertaken. Thus, whereas we have seen that splenectomy caused a quick and marked improvement in 64 per cent. of all patients, natural remissions occurred at one time or another in over 80 per cent. of the patients of Cabot's[5] series treated by the older conservative methods. One cannot maintain from this that perhaps the improvement after splenectomy was only a coincidental remission, because the onset of improvement was too closely and constantly related to the postoperative period; but it does offer some basis for the contention that other methods of treatment may yield results as striking as those following splenectomy. However, from the aspect of duration of the disease the evidence is more

5. Cabot, R. C.: Modern Medicine, Ed. 2, iv, 639.

in favor of the splenectomized series. In Cabot's series, almost half died in the first year of the disease, and of the remainder, one third died in the next year. As the duration of the disease in the splenectomized series had already averaged one and a half years before operation, they should be more properly compared with the remainder of Cabot's group. By the end of the first year conditions in the splenectomized group were as follows: Of thirty-three patients surviving the operation, twenty-four were still improved, three had failed to show improvement or had relapsed to their preoperative condition and six had died. If postoperative deaths, however, were to be included, only about half of those whose fate was known were still

TABLE 8.—RESULTS ACCORDING TO AGE OF PATIENT, BASED ON ONE HUNDRED AND TWENTY-ONE CASES

Age, Decade	Number Cases	Postoperative Results			Subsequently Died
		Deaths	Not Improved	Improved	
3d	8	2	1	5	1
4th	23	4	2	17	2
5th	43	5	2	36	8
6th	28	4	5	19	6
7th	9	5	2	2	1

alive at the end of the first year. From both these points of view, therefore, there are no clear indications as to the value of splenectomy.

The changes in the blood picture after splenectomy are striking and fairly constant. Forty-seven cases are stated to have had a distinct postoperative blood crisis (appearance of normoblasts, megaloblasts, reticulated erythrocytes, Jolly bodies, etc., in larger quantities); and as statements that the blood crisis failed to appear are very rare, it is fair to assume that such a phenomenon is at least a frequent occurrence. In most of the patients who recovered the stimulation forms soon grew fewer in number and coincident with the signs of general improvement the hemoglobin and red cell count rose. The color index, however, usually remained high. As might be expected, also,

the nucleated forms became fewer or disappeared; and yet statements are almost unanimous that the microscopic features of the blood (tendency to macrocytosis, poikilocytosis, etc.), even in many cases that showed almost normal counts, remained suggestive of pernicious anemia. Those patients who died within the first six weeks after operation showed either very slight increase in the blood picture or an actual deterioration; whereas death occurring after that period was in many cases preceded by a distinct improvement in the blood picture with the usual signs of a remission.

TABLE 4.—RESULTS ACCORDING TO DURATION OF DISEASE, BASED ON NINETY-FIVE CASES

Duration	Number of Cases	Postoperative Results			Subsequently Died
		Deaths	Not Improved	Improved	
Under 6 months.....	17	4	..	13	...
Six mos. to 1 year.....	26	4	3	19	3
One to 2 years.....	36	3	6	27	8
Over 2 years.....	16	6	1	9	4

Those few patients who up to the present time have continued well after operation must also be taken into consideration. By the older methods of treatment, Cabot in the first edition of Modern Medicine stated that six out of 1,200 cases after six years of health might be said to have been cured. In the second edition this number was reduced to three. May it not develop that a larger percentage of such "cures" will follow splenectomy, even though the blood picture does not return absolutely to normal? Another point brought out by study of the blood picture at the time of operation is that if the operation is undertaken before the blood has reached an extreme degree of deterioration, not only is the operative risk lessened, but the improvement is greater and more lasting. In any case it is wise to precede it with one or more transfusions.

The average age of the patients at the time of operation was 45; the average duration of the disease at that time 1.6 years. Sex has not been found to exert any influence on the results. If the results are analyzed in groups subdivided according to age, it appears (as one would expect) that less favorable results are obtained in patients in the sixth and seventh decades. A similar arrangement on the basis of duration of the disease, shows that the best results are obtained (after the operation has been successfully passed) in those patients who have had the disease for less than one year.

When arranged according to the degree of anemia at the time of operation, one fact is patent, that the operative risk is much greater in those cases in which hemoglobin is below 20. This is, of course, for this disease, a lower level even than that of one million erythrocytes.

Except for this point, on account of the great fluctuations in blood counts incident to the disease and following transfusions, it is difficult to estimate whether or not the previous condition of the blood has any marked effects on the result obtained. The impression is gained, however, that the best results follow splenectomy in those cases that are not extremely anemic at the time of operation and that have shown considerable fluctuations in the blood picture.

Information as to the size of the spleen was secured in eighty-nine cases. In twenty-eight cases (31 per cent.) the spleen was either small or approximately normal in size. In forty-one cases (46 per cent.) the spleen was slightly enlarged (between 250 and 500 gm.); and in twenty cases (23 per cent.) it was considerably enlarged. In other words, although seldom palpable before operation, it was distinctly enlarged in over two thirds of the cases. If the results of splenectomy are subdivided according to the size of the spleen, it will be seen that better postoperative results were obtained in the cases with enlarged spleens. The

third group in this arrangement, however, is the only one that could be said to have fared better than another as regards the ultimate outcome of the disease.

THE EFFECT PRODUCED BY SPLENECTOMY

Whatever the cause of the distinct improvement after splenectomy in those patients who survive the operation, it is obvious that it is not due to the removal of the sole cause of the disease. If Eppinger's theory of thickened arteriole walls in the spleen with consequent damming back and destruction of red cells in the splenic pulp were correct, removal of the spleen should indeed cure the disease; but our studies show that this

TABLE 5.—RESULTS ACCORDING TO PREOPERATIVE DEGREE OF ANEMIA, BASED ON ONE HUNDRED AND FOURTEEN CASES

Hemoglobin	Number of Cases	Postoperative Results			Subsequently Died
		Deaths	Not Improved	Improved	
Below 20	9	7	1	1	...
Below 30	29	6	2	21	3
Below 40	33	2	2	29	7
Above 40	43	7	7	29	5

is not the case. On Eppinger's theory, also, the characteristic remissions of pernicious anemia would be difficult to explain.

The postoperative blood crisis discussed above, and the subsequent improvement in the blood picture, decrease in urobilin, etc., indicate both that a stimulus has been applied to the bone marrow and that a source of blood destruction has been removed. Lee's findings of an increased number of platelets after splenectomy would also support the bone marrow stimulation theory. Hypotheses to explain these phenomena have been unsatisfactory and the relevant experimental evidence often contradictory. Klemperer believes that the bone marrow activity is induced by removal with the spleen of an inhibiting hormone, but from experiments in our laboratory we have found (in normal

animals, to be sure) not only that this bone marrow activity does not occur until after several months have elapsed (Pearce and Pepper[6]) but also that fresh splenic extract stimulates instead of inhibiting the bone marrow (Krumbhaar and Musser[7]). The cause for the blood crisis, therefore, must probably be sought elsewhere; perhaps, as has been suggested, in bone marrow stimulation from metabolic products or from abnormal constituents of the erythrocytes that are allowed to remain in the blood by the removal of the spleen (Decastello). It is also difficult to prove that the lessened hemolysis after splenectomy, as shown by decrease output of urobilin, is actually due to the absence of the spleen. Neither normal spleens nor those removed at operation in cases of blood disease (Coleman, Stewart) can be shown to possess demonstrable hemolytic activity, and studies of the blood entering and leaving the spleen have also failed to throw light on this supposed function of the spleen (Krumbhaar and Musser[7]).

Another factor to be considered is changes in the red blood cells themselves. In one case that I had an opportunity to study (Stewart's), the resistance of the erythrocytes was distinctly increased after splenectomy, so that this might constitute one of the factors of improvement after operation. A similar increase in the resistance of the erythrocytes has been found after the removal of the spleen in normal animals (Pearce and Karsner[8]) and in other blood diseases, but has been denied in some cases of pernicious anemia (Moffitt).

Whatever the cause of the improvement, it is highly probable that the subsequent deterioration is due to other related structures taking over the functions of the spleen (hemolymph nodes, accessory spleens, Kupfer cells in the liver, and perhaps ordinary lymph nodes), although here also no positive evidence has as

6. Pearce, R. M., and Pepper, O. H. P.: Jour. Exper. Med., 1914, xx, 19.
7. Krumbhaar, E. B., and Musser, J. H.: Jour. Exper. Med., 1914, xx, 108.
8. Pearce, R. M., and Karsner, H.: Jour. Exper. Med., 1912, xvi, 769.

yet been produced. Assuming that the cause of the disease has not been removed, the logical sequence would be that when these auxiliary organs have sufficiently developed, the interrupted course of the disease would be resumed.

As to the few patients who up to the present time have continued well after operation, if the curative action of splenectomy is denied, one must assume either that the causative factor has for reasons unknown ceased to operate, or that the auxiliary organs have failed to develop into pernicious activity.

INDICATIONS FOR SPLENECTOMY

In what cases of pernicious anemia, then, should splenectomy be undertaken? One of two lines may be followed, and it is as yet too early to say which, if

TABLE 6.—RESULTS ACCORDING TO SIZE OF SPLEEN, BASED ON EIGHTY-NINE CASES

Size of Spleen	Number of Cases	Postoperative Results			Subsequently Died
		Deaths	Not Improved	Improved	
Normal or diminished	28	9	5	14	2
Slightly enlarged.....	41	5	4	32	9
Considerable enlarged	20	1	1	18	8

either, is correct. If splenectomy merely induces a remission, and this is at present the opinion of the majority of observers, it should be logical to undertake it only as a last resort, when all other measures have proved unavailing, and only with the hope of prolonging life. Even under such limitations, however, the procedure has already proved its value, and in several cases moribund patients have been brought back to life of comparative well-being for many months. Assuming, on the other hand, that an occasional patient may be, for practical purposes, cured of the disease, and giving due weight to the view that greater and longer continued improvement is obtained if the operation is performed before the disease has reached its final stage, it would then be advisable to undertake it

as soon as possible. Another factor that may prove to be decisive is whether or not increased hemolysis can be proved. In those cases with clinically enlarged spleens, icteroid appearance and increased urobilin output, without increased resistance of the erythrocytes, the prognosis is distinctly more favorable than in the opposite types. The condition of the bone marrow is also important, splenectomy being contraindicated if the bone marrow is persistently aplastic. It has also been a matter of clinical observation that those individuals in whom spinal cord symptoms have already developed are less apt to be helped by the operation.

CONCLUSIONS

1. Of the 153 patients studied, 19.6 per cent. died within six weeks; a distinct improvement in the clinical condition and in the blood picture occurred in 64.7 per cent., and no improvement in 15.7 per cent.

2. The rather high postoperative mortality (practically 20 per cent.) may be due to poor choice of cases in the early series. As a much greater proportion of the more recent cases has survived the operation, the true postoperative mortality is probably much less than 20 per cent.

3. Of the individuals who showed improvement shortly after operation, nearly two thirds of the total number, a large number have failed to maintain this improvement, or have since died in a relapse or from intercurrent disease.

4. Although a few have continued in good condition during the period of observation (over two years), in no case can it be said that a cure has been effected, and the blood of these individuals continues to show many of the characteristic signs of pernicious anemia.

5. On account of the improvement that follows splenectomy, it would appear to be not only a justifiable, but in many cases an advisable, procedure; but in no case should a cure be promised or the operation undertaken except under the most favorable conditions.

6. The best results are obtained if the operation is preceded by one or more transfusions, and those patients who relapse after operation may still be greatly helped by transfusion. Whether or not transfusions would have produced equally good results in the absence of splenectomy is a question that cannot at present be decided.

7. The most favorable results may be expected in individuals who have not passed the fifth decade, in whom the disease has not progressed for more than a year, and who have a relatively good blood picture, (that is, an anemia that is not of too extreme a degree or of the steady, progressive type). Individuals with enlarged spleens have done better than those in whom the spleen was small or of normal size, as have also those suffering from an anemia characterized by excessive hemolysis.

8. The opposite of these conditions should be considered as unfavorable factors, as should also the existence of spinal cord symptoms or the presence of an aplastic bone marrow.

SPLENECTOMY IN SPLENIC ANEMIA, HEMOLYTIC ICTERUS AND HANOT'S CIRRHOSIS

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The value of splenectomy in splenic anemia remains unquestioned, and since the first report by Banti in 1894 sufficient time has now elapsed to enable us to draw definite conclusions regarding not only the immediate success, but also the permanency, of the results. Within recent years two other conditions resembling in many clinical aspects splenic anemia have been relieved and probably permanently cured by splenectomy, namely, hemolytic icterus, both of the acquired and congenital type, and the hepatic cirrhosis of Hanot. These three conditions, splenic anemia, hemolytic icterus and the cirrhosis of Hanot, have many things in common and no doubt in the past have been frequently confused.

In all there is marked enlargement of the spleen, although the literature contains a few reports of apparently true hemolytic icterus without palpable splenic tumor. In all three conditions there is chronic anemia or chronic icterus, or both. Evidence of obstructive icterus is always lacking, and when jaundice is present the patients do not show certain toxic manifestations, as bradycardia and pruritus, so common in other forms of jaundice. While typical hemolytic crises occur in only hemolytic icterus, sudden, unaccountable increase in the anemia is not infrequent in Banti's disease. Hemolytic icterus often occurs in several members of a family and may be definitely hereditary.

While familial cases are much less frequent in splenic anemia, they nevertheless occur; in fact, the Gaucher's type of splenomegaly, which must be classed with splenic anemia, quite frequently takes this form; and Brill, Bovaird Collier and others have reported two or more cases of splenic anemia in the same family, and White reports 104 cases of splenomegaly with anemia from South China, where he states the condition is common and is often a family disease. To show the close relation between these two conditions, Chauffard and Troisier report a case in which the mother of the patient had hemolytic icterus, the son had an enlarged spleen with anemia and no icterus, but with urobilin in the urine and lessened resistance of the red corpuscles. The writer recently saw an apparently typical case of hemolytic icterus, but without enlarged spleen, the patient reporting that his sister had a large spleen, which had been removed, but she had never suffered from icterus.

Chronic jaundice is constantly present in hemolytic icterus and Hanot's cirrhosis, but it is infrequent in splenic anemia. Osler reports its presence in only four of his twenty-six cases, and Griffin in two out of eighteen cases. Great enlargement of the liver is constantly present in Hanot's cirrhosis, and a very decided enlargement of the liver is not infrequent in hemolytic icterus. Osler, in sixteen cases of splenic anemia, reports moderate enlargement of the liver in six, and in one the liver was very decidedly enlarged.

The chief point of difference in these three conditions is the lowered resistance of the red corpuscles in hemolytic icterus. This finding, however, is not constant and its absence should not interfere with the diagnosis of hemolytic icterus in the presence of other evidence. Normal resistance of the erythrocytes has been reported in two cases by Hopkins, two by Lommell, one by Claus and Kalberlak, all of these being of the familial type. Morse reports two and Banti one of the acquired form. Türk states that in splenic

anemia the resistance of the red corpuscles may be increased or diminished, and Eppinger reports three cases, all with increased resistance. In Hanot's cirrhosis, as in other forms of chronic icterus, the resistance of the red corpuscle is increased.

In hemolytic icterus bile is usually present in the blood, but there is no urobilin; while in the urine bile is absent except during hemolytic crises, but urobilin is present. This peculiar condition is not present in either of the other two diseases.

Secondary anemia of greater or less degree is characteristic of splenic anemia and hemolytic icterus, but is not present in Hanot's cirrhosis.

Urobilin in the stool, usually considered as an index of blood destruction, is greatly increased in hemolytic icterus. Eppinger believes that the amount present in the normal stool is from 0.12 to 0.15 gm., while in three patients with hemolytic icterus the amount varied from 2.25 to 3.8. Eppinger and Robertson have each determined the urobilin in the stool in Hanot's cirrhosis and they find it varies little from the normal. Eppinger has reported on two cases of Banti's disease, the amount of urobilin being 0.32 and 0.33 gm., respectively, a rather moderate increase above the normal and often reached in various conditions, as, for instance, in cardiac incompensation. That blood hemolysis is not especially important in splenic anemia is further supported by the relatively small amounts of iron found in the liver, spleen and kidneys in this condition. There is also no evidence that blood hemolysis is active in Hanot's cirrhosis, while in hemolytic icterus excessive blood destruction is very evident.

In these three conditions, which are in many ways so closely related, it is at present impossible to explain why in Hanot's cirrhosis there is icterus without anemia, in splenic anemia there is anemia without icterus, and in hemolytic icterus there are both icterus and anemia, although in many instances icterus is the dominant condition.

Splenic Anemia.—The majority of modern writers question whether we have in splenic anemia a disease entity. It is quite probable that in the past some patients with hemolytic icterus were diagnosed as having splenic anemia. It is also quite likely that at present splenomegaly of varied etiologic origin is included in this group. Banti's original definition included only those cases of anemia with enlarged spleen in which known etiologic causes could be excluded. It is not improbable that a chronic splenic tumor from any cause, especially if this enlargement is associated with great increase in the endothelial cells, which have been shown to have a marked erythrolytic activity, might give rise to chronic anemia. That in such cases splenectomy might be curative is also probable. Gaucher's splenomegaly may be given as a type of splenic anemia. Clinically, it conforms satisfactorily with our conception of splenic anemia. The histologic condition of the spleen, however, places it in a distinct class. Especially in children splenomegaly from syphilis with anemia may also be included, at least clinically, as splenic anemia. Chiari and Marchand report evidence of syphilis in some patients with clinically diagnosed splenic anemia coming to necropsy. Caronia applied the Wassermann test to the parents of thirty children with splenic anemia and reported it positive in nineteen. Curshmann reports the case of a patient with a history of hereditary syphilis who clinically had splenic anemia, recovery occurring after salvarsan. Mayo refers to three patients in whom syphilis may have been the cause.

In somewhat the same manner the enlarged spleen in a case of cured malaria might take on an increased erythrocytic function and thus give clinically a splenic anemia. Bey reports three cases, two corresponding to the first stage of Banti's and one to the third stage, that cleared up completely under quinin. In all of these there was a definite history of malaria. Throm-

bosis of the splenic or portal vein, with stenosis, may also give rise to clinical splenic anemia, as in the case reported by Warthin and Dock.

The classification of all splenic tumors with chronic anemia under the general head of splenic anemia may not be logical, but from a therapeutic point of view such a grouping may be desirable, as there is indisputable evidence that cure has been effected in the vast majority of patients clinically diagnosed as having splenic anemia, on whom splenectomy was performed. Even when the disease had advanced to the point of marked hepatic cirrhosis and ascites, more or less complete return to normal has been reported.

The results of operative measures in the early stage of the disease are excellent. Griffin, from the Mayo Clinic, reports the cases of five patients, three with cirrhosis and ascites, and two in the preascitic stage of cirrhosis, on whom splenectomy was performed, and four of the five returned to normal health. One of these patients with ascites has been well seven years. In the Mayo series of eighteen patients, two died, or 11 per cent. Twelve of the sixteen recovering from the operation are now in excellent health (1915); two are definitely improved; one at first improved, later developed ascites and died, and one died two years after the operation, the cause of death not being determined. Some have advised against splenectomy during the ascitic stage, but the literature contains several reports, in addition to those already referred to, of the disappearance of ascites after splenectomy and the permanent cure of the patient. As operation is the only means that offers hopes of cure in this disease, it should be undertaken, provided the condition of the patient is not such as to make recovery from the operation improbable.

Regarding the mortality from splenectomy, the figures of Mayo have already been given, 11 per cent. in eighteen cases. This represents the lowest reported operative mortality in a relatively large series of cases.

In the thirty-six cases reported by Banti, in which splenectomy was performed, the mortality was 44.4 per cent. Fifty-seven cases from various sources between 1900 and 1909 gave a mortality of 19 per cent., and in sixty-one cases reported since then the mortality was the same. This may probably be taken as the average mortality. In addition to the reported cures of splenic anemia by mercury and quinin, distinct benefit has been observed in a number of cases through the use of the Roentgen ray. There is no definite evidence, however, that any of these have been permanently cured.

Hemolytic Icterus.—Minkowski in 1900 was the first to describe this condition as a distinct disease. Appearing either as an acquired or familial condition, the first symptoms may develop either at birth or during early adult life. The characteristic symptoms, outside of its familial nature, are the chronic icterus of fluctuating intensity, combined as a rule with varying degrees of anemia; greatly enlarged spleen, often moderately enlarged liver, urobilin in the urine, but no bile except in some instances after a hemolytic crisis; the stools well colored, with no evidence of biliary intoxication, ás pruritus and bradycardia, and the presence usually of a lowered resistance of the red corpuscles. The disturbed resistance of the erythrocyte, which has been considered so characteristic of this condition, is not always present. Banti, Claus, Morse, Lommell and Hopkins have reported cases of both the hereditary and acquired types with normal corpuscular resistance. Even absence of a splenic tumor has been observed by Banjamin and Sluker, Marchiafavas and Nazarios, and the writer has recently seen a case of this character.

As a rule the patient is little inconvenienced by his trouble, so that Türk has referred to it as a cosmetic disturbance, rather than a disease. Probably too much stress has been placed on the benign character of the trouble, as the majority of these patients suffer from

anemia and consequent lowering of their efficiency. Especially following a hemolytic crises, the occurrence of which is so common in these cases, the degree of anemia may be so great as to temporarily incapacitate the individual. In a case recently observed the hemoglobin fell during a crisis from 85 to 40 per cent., the patient developed a temperature of 105 and for two days was delirious. It is true that the degree of inconvenience observed varies greatly; some are apparently not the least disturbed by their condition, others are always under par. Symptoms, when present, are due to the anemia, and not to the icterus. When considering the advisability of splenectomy, the degree of inconvenience caused by this trouble should be seriously considered, as the operation is attended with a certain amount of danger and should not be undertaken without definite indications.

The usual presence of lowered resistance of the erythrocytes and the relation of the spleen to this phenomenon stamp hemolytic icterus as having a probable etiologic relation to the spleen. The hemolytic function of the normal spleen was first described by Kolliker in 1847, and Balbi in 1893 reported that splenectomy increased the resistance of the red corpuscles. In 1895 Banti demonstrated that in dogs after splenectomy pyradin did not cause icterus. This work has been confirmed by a large number of observers — Pel, Paton and Goodall, Pearce, Heinz and others. It might be considered that as the normal spleen tends to lower the resistance of the erythrocyte to hemolytic agents, an enlarged or hyperfunctioning spleen might increase this tendency to such a degree that hemolysis would occur from a variety of mildly hemolytic agents normally present. It is possible in these cases, however, that the enlarged spleen may not be the cause of the disturbed resistance of the erythrocyte, as it is well established that this disturbed resistance is not always present. Furthermore, while as a rule the resistance of the corpuscles soon returns to normal

after splenectomy, there are several cases on record in which this failed to take place. A notable case of this kind is seen in the patient operated on in 1887 by Sir Spencer Wells, in whom, as reported by Dawson, the red corpuscles still showed lessened resistance in 1914. Roth also reports a case in which three and one-half years after splenectomy the corpuscles hemolyzed in 0.6 per cent. salt solution. It is possible these patients may have developed accessory spleens. Küttner reports a case in which necropsy, made eleven years after splenectomy for gunshot wound, revealed the presence in the peritoneal cavity of eighty to one hundred spleens. Significant, however, is the fact that in spite of the disturbed resistance of the erythrocyte these patients after the splenectomy have remained well, showing that the spleen is responsible in some way for the hemolysis, even if not concerned in the lowered resistance of the red corpuscles.

Splenectomy is undoubtedly curative. Although Micheli in 1911 was the first to perform splenectomy in recognized hemolytic icterus, several patients wrongly diagnosed as having splenic anemia had been previously splenectomized with permanent cure. In this list might be mentioned Banti's case in 1904, Umber's in 1904, Burghard and Sutherland's in 1906, and Roth's in 1908. Since Micheli's case the number of reported splenectomies has grown rapidly. Elliott and Kanavel in 1915 collected in the literature forty-eight cases. The operative mortality in these forty-eight cases was only 4.1 per cent., surprisingly low. The forty-six patients who recovered from the operation were cured. The jaundice rapidly disappeared, beginning within a few days, and as a rule being complete within two weeks. The recovery from the anemia was somewhat slower, but relatively rapid. The hemolytic crises ceased, although Elliott and Kanavel report a crisis in their patient fifteen days after splenectomy. As only five years have elapsed since Micheli's case, it might be said that time has been too

short to insure permanency. In the list of permanent cures, however, may be included those cases already referred to in which splenectomy was performed under a different diagnosis. As none of these patients have relapsed, we are justified in saying the results are permanent.

Parisot and Huelly in 1913 report two cases of hemolytic icterus cured by the Roentgen ray; the permanency of these results cannot be confirmed. With our knowledge of this condition it is reasonable to believe that the Roentgen ray may be beneficial.

Hanot's Cirrhosis.—True Hanot's cirrhosis is a rare disease. Like splenic anemia, mistaken diagnoses are probably frequent. That it bears some resemblance to splenic anemia and hemolytic icterus must be admitted. For this reason it is not surprising that a cure should follow splenectomy. Eppinger in 1913 reported two patients cured and Mayo recently reported one. As far as I have been able to determine, these are the only reported cases. It would appear probable, however, that in Hanot's cirrhosis, a condition which has heretofore been considered incurable, splenectomy was indicated.[1]

1. Those interested in consulting the literature on this subject will find a very complete bibliography on both splenic anemia and hemolytic icterus in the following artcles:
Krumbhaar: Analysis of Clinical Types of Splenomegaly Accompanied by Anemia, Am. Jour. Med. Sc., 1915, cl, 227.
Elliott and Kanavel: Splenectomy for Hemolytic Icterus, Surg., Gynec. and Obst., 1915, xxi, 21.

SPLENECTOMY FOR HEMOLYTIC JAUNDICE

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The past few years have shown a great increase in the interest manifested by American surgeons in the surgery of the spleen. Splenectomy has been demonstrated to be a safe and effective means of curing certain diseases (for example, Banti's disease), and is extensively employed in other conditions in which its ultimate benefit still has to be proved by a more prolonged study and report of late results.

Among the conditions which seem to be promptly and permanently benefited by splenectomy is the group of so-called hemolytic jaundice cases, which occur in two forms, the congenital and the acquired.

The accumulating evidence of the results of splenectomy has proved the etiologic relation of the changes in the spleen to the disease. The former hypothesis of essential hemolysis must be abandoned. What the exact nature of the process may be is still more or less obscure, but that the spleen plays the most important part is certain. The constant presence of urobilin and urobilinogen in the urine is simply an evidence of the destruction of the hemoglobin molecule in the process of hemolysis, and these substances disappear soon after splenectomy is performed.

No bile is found in the urine unless there is a complicating disease of the biliary tract. This complication has been noted many times.

In the congenital group we have the well-recognized familial type, in which heredity plays such a striking part, and also congenital cases, in which no family his-

tory exists, but in which the jaundice appears at birth or in early infancy and persists throughout life or until relieved by operation.

The acquired type forms another distinct clinical group, the symptoms of which closely follow those of the congenital type. We have had three typical cases in patients on whom splenectomy has been performed in the second surgical division of the Roosevelt Hospital, since May, 1912, when the first case to be reported came under my care. The patient, a young woman, aged 30, of the congenital, nonfamilial type, was the first patient on whom splenectomy was performed for congenital hemolytic jaundice in this country.

Her history was as follows:

F. N. (history No. B2654), a married woman, aged 30 years, on May 6, 1912, was admitted to the second surgical division of the Roosevelt Hospital, transferred from the medical service of Dr. Evan Evans. Her only complaint was a mild degree of persistent jaundice, she being otherwise healthy. She was one of a family of eleven, her father, mother, three brothers and seven sisters being alive and well. None of them had ever been jaundiced, nor was there a history of jaundice in any branch of her family. She was the first child, born at full term in normal labor. Jaundice was first noticed when she was 3 days old, and this had continued all her life. She had measles, mumps and whooping cough as a child, but no other illnesses. Her appetite was good, she slept well, took plenty of exercise and drank no alcohol, and coffee and tea only moderately.

The jaundice was present in mild degree with no other symptoms until she was about 21 years of age, when she first had an attack of deepening of the jaundice. Since that time similar periodic attacks (acholuric crises) have occurred, with a general tendency to deepening of the jaundice, but with no other symptoms. She has never had itching, slowing of the pulse, or any of the symptoms which accompany an ordinary obstructive jaundice.

In July, 1907, in Baltimore, cholecystostomy was performed, but no gallstones or other lesions of the biliary tract were found. Jaundice returned and persisted as before as soon as the biliary fistula healed.

On January 22, 1909, two and one half years after the cholecystostomy, she was admitted to the Johns Hopkins Hospital, and was under observation by Dr. Thayer for about two weeks. A diagnosis of congenital hemolytic jaundice was made by Thayer,[1] who did not advise operation. Her

1. Thayer and Morris: Bull. Johns Hopkins Hosp., 1911, xxii, 85.

red cell fragility tests at that time were practically identical with those taken by us three years later. Thayer stated in his comments that "in congenital hemolytic jaundice recovery is unknown, but some improvement may be obtained by persistent treatment with iron." Pathologic changes in the spleen and splenomegaly were recognized, but their definite relation to the etiology of the disease was not appreciated, and the cause of the fragility and increased hemolysis was thought to reside in the blood itself. From Jan. 26 to Feb. 11, 1911, she was in a hospital, in New York, again for the jaundice. A diagnosis of congenital stenosis of the common duct was now made, but operation was not advised. From July 16 to Aug. 14, 1911, she was under treatment in the same hospital, ill with typhoid fever, and from August 18 to September 12 she was back with a relapse.

The persistence of the jaundice so preyed on her mind that on March 5, 1912, she was again operated on, at the Roosevelt Hospital, first surgical division, in the hopes of finding calculi or some lesion of the biliary tract. No calculi were found, and no lesion of the gallbladder or ducts; a few whitish spots on the surface of the left lobe of the liver were seen, and one was excised for examination. It showed simply anemic, degenerated liver cells. The operation was a simple exploration. On April 10, 1912, she was readmitted to the Roosevelt Hospital, medical division, service of Dr. Evans. Careful studies were made by Dr. Evans and Dr. Mortimer Warren, pathologist to the hospital, whose report, which follows, covers the periods before and after splenectomy.

The jaundice was general, of a moderate degree, lemon yellow in color, lacking the greenish tinge of obstructive jaundice. The edge of the spleen was 4 to 6 cm. below the costal margin.

Urobilin was present in the urine, but no bile. Bile was present in the feces, which were of normal color. The Wassermann reaction was negative.

Blood examination showed hemoglobin 63 per cent., red blood cells 4,400,000, and white blood cells 8,000. The differential count showed polymorphonuclears 65 per cent., lymphocytes 20.5 per cent., large mononuclears and transitionals 10.5 per cent., eosinophils 3.5 per cent., and basophils 0.5 per cent. The red cells were small and of good color, and there were no nucleated red cells. Plates were abundant. About 20 per cent. of the red cells showed postvital reticulation. Five fragility tests taken between March 16 and April 22, 1912, before splenectomy, showed, as an average, a minimum resistance of 0.72 per cent., and a maximum resistance of 0.27 per cent. On May 9, two days after splenectomy, test showed a minimum resistance of 0.72 per cent., and a maximum of 0.36 per cent. Four tests taken from May 13 to May 25, 1912, six to eighteen days after splenectomy, gave as an average a minimum resistance of 0.50 per cent.,

and a maximum of 0.32 per cent. Test made Sept. 9, 1912, four months after splenectomy, gave a minimum resistance of 0.48 per cent. and a maximum of 0.30 per cent. Test Oct. 8, 1915, three years and five months after splenectomy, showed a minimum resistance of 0.40 per cent. and a maximum of 0.35 per cent. The hemoglobin, which was 65 per cent. two days after splenectomy, reached 80 per cent. on June 7, 1912, one month later. The red blood cells, at first slightly reduced, were about normal. Red blood cells showing postvital reticulation appeared only in moderate (normal) numbers after operation. On May 9, 1912, two days after splenectomy, examination showed leukocytes 30,000, polymorphonuclears 80 per cent. On Oct. 9, 1912, four months after operation, examination revealed leukocytes 11,000, polymorphonuclears 53 per cent., lymphocytes 22 per cent. Examination of blood Oct. 18, 1915, three years and five months after operation, gave as a result, hemoglobin 95 per cent., red blood cells 4,204,000, white blood cells 13,000, polymorphonuclears 58 per cent., lymphocytes 30.3 per cent., transitionals 7.9 per cent., eosinophils 3.6 per cent., with plates abundant. The red blood cells showing postvital reticulation were 0.5 per cent.

On the advice of Drs. Evans and Warren, and in the belief that pathologic changes in the spleen were responsible for the excessive hemolysis, and possibly for the fragility of the red cells, splenectomy was performed on May 7, 1912. There were no adhesions, and the operation was technically simple and well borne.

The spleen was only moderately enlarged, weighing 360 gm. and measuring 19 by 12 by 6 cm. Gross section showed no evidence of pathologic change beyond congestion, except for the presence of numerous light-yellow, firm nodules from 1 to 4 mm. in diameter. The surface was roughened with many light-colored pinpoint spots scattered over the surface.

Microscopic examination showed marked congestion, with much of the blood interstitial. There was no marked increase in fibrous tissue. The arterioles appeared thickened, and nodules were noted in areas of sclerosis, showing with proper stain remains of elastica. They were, therefore, sclerosed arterioles, possibly the result of typhoid. Follicles were somewhat crowded out.

A diagnosis was made of congestion of the spleen, chiefly interstitial. Except for a mild, left-sided pleurisy, with effusion, which developed on the sixth day and lasted about a week, convalescence was uninterrupted. Diminution in the jaundice could be definitely noted on the third day after operation, and by the tenth day, for the first time in her life, she was entirely free from jaundice, and has remained so ever since. The prompt and permanent disappearance of the jaundice, together with the great improvement in the red cell resistance, has been most satisfactory.

This case presents several striking features, among which was the marked degree of fragility of the red cells before operation and their prompt return to the normal after splenectomy, a result which has been by no means uniform in the reported cases. Another was her rather checkered surgical experience, owing to the fact that her treatment coincided with the developmental stage of our knowledge of the condition, and of the etiologic relation of the diseased spleen to it. As Chauffard so aptly remarks, "she was more icteric than sick," but in spite of this fact, the presence of the jaundice and the feeling that she was different from other healthy women so preyed on her mind that she persisted in her efforts to find a cure for her malady.

The case presented the characteristic findings of hemolytic jaundice, as described first by Hayem[2] in 1898, by Chauffard[3] in 1907, and by Elliott and Kanavel[4] in their interesting case of the familial type. and many other careful observers, namely, persistent, nonobstructive jaundice without itching, slowing of the pulse or the presence of bile in the urine; paroxysmal exacerbations of the jaundice, at times accompanied by dull, aching pain in the upper abdomen; chronic splenomegaly of a moderate degree; secondary anemia of a moderate type; fragility of the red cells of a very marked degree, with complete return to the normal after splenectomy; increase in the number of reticulated red cells to 20 per cent., which fell to normal (0.5 to 1 per cent.) after splenectomy; the presence of urobilin and urobilinogen in the urine.

The second case was of the acquired type, of short duration, the patient having had symptoms for only nine months preceding the operation. As has been previously noted in this type, the onset of the jaundice was ushered in by an acute illness, accompanied by fever, after which the jaundice persisted and increased in degree without the occurrence of definite crises.

2. Hayem: Presse méd., 1898, i, 121.
3. Chaffard: Semaine méd., 1907, No. 3, p. 25.
4. Elliott and Kanavel: Surg., Gynec. and Obst., 1915, xxi, 21.

In contrast to the preceding case, the red cell fragility in this case was not very marked, and did not change perceptibly after splenectomy. The vital stain reticulation of the red cells reached 16 per cent. and dropped to normal after operation. The secondary anemia was moderate in degree, the hemoglobin and red cell count approaching the normal soon after operation. Auto-agglutination tests were negative, as in Michelis' case, in contrast to the experience of Widal, Abrami and Brulé,[5] who found it constantly positive in the acquired type, and absent in the congenital and familial types. Urobilin and urobilinogen were present in the urine, and the feces were normal in color and contained bile. Splenomegaly was pronounced, the spleen weighing 800 gm. Splenectomy was followed by a prompt disappearance of the jaundice and a complete return to health.

An abstract of this patient's history follows, and further detailed studies of the case have been published by Dr. G. A. Friedman, from whose service at the Vanderbilt Clinic he was referred to me for operation.

M. T. (history No. B7036), an Italian, a single man 18 years of age, was referred from the Vanderbilt Clinic early in November, 1915, where he had been carefully studied by Dr. G. A. Friedman, who made a diagnosis of acquired hemolytic jaundice and advised splenectomy. Except for diseases of childhood, the nature of which he did not know, the patient had had no previous illness. He had come to America from Italy eighteen months before. Jaundice was first noted about nine months before he came to the hospital, and had been persistent up to the time of admission.

Examination showed a rather slender, well-nourished young man, with marked general icterus of a lemon yellow hue. His spleen extended to within an inch of the umbilical level in the mammary line.

The urine contained urobilin and urobilinogen; the feces were of normal color and contained bile and also urobilin.

The blood examination showed a moderate degree of secondary anemia; 78 per cent. hemoglobin; 4,200,000 red cells, with 16 per cent. postvital reticulation, and a normal differential count. Auto-agglutination tests were negative. Two

5. Widal, Abrami and Brulé: Presse méd., 1907, lxxxi, 641.

fragility tests before operation showed a minimum resistance of 0.48 to 0.50 per cent., and a maximum resistance of 0.30 to 0.35 per cent.

Splenectomy was performed on November 23, 1915, at the Roosevelt Hospital. The gallbladder and ducts, liver, stomach and pancreas were normal. The spleen measured 17 by 10 by 7 cm. and weighed 800 gm. It was slightly adherent along the posterior border and at the upper pole, but delivered without great difficulty and the operation was well borne.

The jaundice began to fade within two or three days and was entirely gone by the tenth day. The patient has remained well and entirely free from jaundice since the operation.

The spleen was rather soft and flabby, the cut surface was dark red and rather granular, and the trabeculations stood out prominently. Microscopically, there was no increase of fibrous tissue; the follicles were of varying size, some having disappeared. There was marked interstitial suffusion with red blood cells. The changes in the pathology of the spleens removed have been fairly uniform and correspond with those found in previous reports. There is marked interstitial suffusion of red blood cells, dilatation of splenic sinuses, loss of follicles and absence of germinal centers. There is practically no increase of fibrous tissue.

Six days after splenectomy the fragility test showed a minimum resistance of 0.50 per cent. and a maximum of 0.35 per cent., that is, there was no change following the operation. On December 20, four weeks after operation, the fragility test was the same, reticulation of the red cells was normal (0.5 per cent.), and urobilin and urobilinogen had disappeared from the urine. The patient gained in weight and resumed his work four weeks after the operation.

This case illustrates the acquired type of hemolytic jaundice, evidently dependent on the splenic changes and on no previous etiologic factor that could be determined.

The fragility of the red blood cells in this case was slight, and was practically unchanged after splenectomy.

The third case was of the congenital, nonfamilial type, and the patient was operated on by my colleague, Dr. James I. Russell, to whom I am indebted for permission to include it in this report. Only a brief abstract of the history will be given, as the case was presented to the New York Surgical Society and reported in its *Proceedings*.

The patient was a man, 20 years of age, transferred from the medical service to the second surgical division on July 6, 1915 (history No. 6546).

He had been jaundiced since birth, the icterus increasing up to 5 years of age, after which time it was stationary. There was no history of jaundice in the family. He presented the following symptoms: Icterus of a fairly marked degree, nonobstructive in type, of a lemon yellow hue, secondary anemia of a mild type; 74 per cent. hemoglobin, 5,200,000 red cells; red cell fragility not increased, the minimum resistance being 0.45 per cent., and the maximum 0.30 per cent., remaining unchanged after operation; reticulated red cells, vital stain, 8 per cent.; splenomegaly of a marked degree, the spleen weighing 1,143 gm.

Splenectomy was performed on July 10, 1915, and was followed by complete disappearance of the jaundice and a prompt recovery.

In addition to the three cases cited, I have recently performed cholecystectomy for calculi with chronic cholecystitis in a typical case of congenital hemolytic jaundice of the familial type, with marked splenomegaly. Both the patient and her physician were unwilling to have splenectomy performed at that time, though recognizing the possible necessity of such a procedure in the future.

That hemolytic jaundice is not uncommon and that it can be cured by splenectomy are now well recognized, and recent contributions to the literature are emphasizing its importance and bringing it more and more to the attention of the profession.

INDICATIONS FOR SPLENECTOMY IN CERTAIN CHRONIC BLOOD DISORDERS

THE TECHNIC OF THE OPERATION

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Splenectomy has already proved a curative measure in certain diseases associated with definite blood changes, and the operation has recently been advocated for other diseases which appear to be more or less closely related to those in which the spleen is now the known causative factor. The basis on which splenectomy has been suggested in these heretofore incurable conditions will be more clearly understood if we briefly review the development which has resulted in the present situation.

Splenic anemia offers the most familiar example of the therapeutic value of splenectomy. Sufficient time has now elapsed since the earlier operations for this disease to prove that the results of splenectomy in early or in moderately advanced cases are not only excellent, but permanent. The most interesting characteristic of the disease as concerns the purpose of this paper is its tendency to develop cirrhotic changes in the liver. In fact, Banti described the disease as it appeared in its later stages when it is associated with marked cirrhosis and with ascites. In such a stage, from a diagnostic standpoint, it is often difficult and sometimes impossible to determine in a given case whether the condition is the result of a true splenic anemia or of a primary liver cirrhosis associated with a large spleen. Experience has shown that in the very late stages of splenic anemia definite improvement fol-

lowing splenectomy cannot be expected, yet it is also true that a moderate cirrhosis, even associated with ascites, has been present in some cases in which excellent results have been obtained. This fact, therefore, with the probability that certain of the cases which have been classified as true splenic anemias and operation performed on that diagnosis, were in reality cases of primary cirrhosis, was responsible for the suggestion that splenectomy might prove of value in arresting the progress of selected types of hepatic cirrhosis.

The interdependence of spleen and liver is not clearly understood, yet there is ample evidence to show that some of the most important functions of the liver, for example, its hemolytic power, are more or less controlled by the spleen. Certain pathologic conditions in the liver, therefore, are the result of overactivity, which may in turn be due to overstimulation by the spleen.

During the last two years, with this theory as a basis, selected patients with primary hepatic cirrhosis have been splenectomized. Two, at least, of four such cases of our own gave promise that the removal of the spleen might stop or retard the progress of the disease, but we are not yet in a position to state the value of such a procedure.

The success of splenectomy in splenic anemia, with associated splenomegaly and severe anemia, has led to splenectomy in other diseases in which splenomegaly and anemia are characteristics. One of the most interesting of these is the syphilitic spleen; we have seen good results follow splenectomy in three cases of this form of syphilis. The prominent clinical features of the cases in which we believed operation to be indicated were (1) splenomegaly, (2) a history of syphilis not responding to treatment, (3) positive Wassermanns, (4) anemia. It is important to note that previous to operation a negative Wassermann could be obtained under appropriate treatment, but the reaction became positive as soon as treatment was dis-

continued. All these patients had gummas in the liver, and in the spleens removed the spirochete could be demonstrated in large numbers. It was also a clinical observation that although the virulence of the infection could be more or less controlled by antisyphilitic treatment, it was not eradicated.

From the foregoing facts, the conclusion may be drawn that the spleen picks up the spirochetes and harbors them, and this conclusion is supported by the surgical observation that removal of the spleen, followed by antisyphilitic treatment, results in prompt and permanent relief.

The influence which the spleen exercises on the hemolytic function of the liver and spleen is most strikingly illustrated in the effect of splenectomy in hemolytic jaundice. Although this disease is a problem from an etiologic standpoint, the most important therapeutic fact is that splenectomy is followed by prompt, complete and permanent cure. The rapid disappearance of the icterus, which is the most obvious symptom of the disease, is an amazing clinical result; the anemia, which is sometimes severe, is also rapidly corrected.

The remarkable results following splenectomy in splenic anemia and hemolytic jaundice, particularly the latter, appear to have provided the basis on which Eppinger and others have suggested that similar surgical treatment might prove of value in pernicious anemia. It is important, therefore, that the relationship of splenectomy to these other diseases should be borne in mind. The argument becomes more forceful if it is possible to establish similarities between any one of these diseases for which splenectomy is curative, and pernicious anemia. Many of the features of hemolytic jaundice appear to have a counterpart in pernicious anemia, and, in fact, Eppinger believes that the chief, and possibly the only, difference between hemolytic jaundice and pernicious anemia is that in the former the bone marrow is able to com-

pensate for the increased blood destruction, whereas in pernicious anemia it soon loses this power, and the disease eventually is dependent on a bone marrow disability.

It would, therefore, appear as a logical sequence that since splenectomy has proved a specific in hemolytic jaundice, it would sooner or later be advocated in pernicious anemia. Although the first operations for this disease were performed, both abroad and in this country, about the same time (1913), to Eppinger must be given special credit for efforts to establish a scientific basis for the surgical treatment. While the surgical therapeusis of pernicious anemia can be considered as on trial, it presents features of much interest and promise, and splenectomy is now being performed with a frequency which should soon permit definite and decisive deductions.

It must, of course, be primarily recognized that any new therapeusis in a disease of the character of pernicious anemia must be subjected to a particularly thorough trial. The extreme chronicity of the disease in its usual course, and the fact that, with or without treatment, remissions occur, during which the patient is much improved and the blood may even revert to normal, stamps any conclusions based on the early results of operation as premature. This much, however, can be said, that immediate improvement follows splenectomy more consistently and promptly than any treatment heretofore used.

It is on the ultimate results, however, which are as yet insufficient, that the final decision as to the real efficiency of splenectomy in pernicious anemia must rest. There is at the present time, therefore, decided uncertainty as to any superior therapeutic value of a permanent character possessed by splenectomy. It is also true that pernicious anemia has thus far been an incurable disease, ranking in fatality with cancer and less amenable to successful treatment. The certainty of the ultimate prognosis has been the outstanding

feature of our knowledge of the disease, and the doomed patient could hope only that the disease would be slowly progressive and not associated with great physical disability.

The pathologic picture which Eppinger has described as distinctive of the spleen in pernicious anemia is as follows: The pulp areas in the spleen, and only these, are gorged with blood. Eppinger explains this engorgement as a direct result of an abnormal condition of the central artery. It has been shown that the entire wall of this artery is greatly thickened, and that the greatest change takes place in the media. The theory is, briefly, that sufficient obstruction results to force the flow of blood through the capillaries into the pulp areas, where the erythrocytes are destroyed. If a constant pathology can be demonstrated in the spleen in pernicious anemia, it will be a great advance toward the rational treatment of the disease.

While it cannot be held that the basis on which Eppinger and his followers have endeavored to establish the surgical treatment of the disease has been confirmed or even well supported by others, it is not essential, nor is it good judgment, to postpone surgical treatment of the disease until an acceptable basis for such treatment is generally recognized.

The hemolytic nature of pernicious anemia is demonstrated by the increased amounts of urobilin and urobilinogen excreted. It has been assumed, and there is much clinical and experimental evidence to show, that this hyperhemolysis is due to a hypersplenism, and interesting investigations are now being conducted, after the suggestion of Schneider, to determine the exact quantity of these hemolytic products by obtaining them immediately with a duodenal tube on their exit from the liver. Giffin has shown, by the records of the urobilin and urobilinogen estimation in a series of cases of pernicious anemia, that the values appeared to run more or less parallel to the degree of icterus, and that in some cases at least there was a marked fall

in the value of the blood-derived pigments after splenectomy. It is possible that from this method information of at least prognostic value may be derived. Giffin has suggested the very interesting possibility that the relation of hemolysis, as shown by the estimation of the blood-derived pigments, and the bone marrow disability, as illustrated by the blood picture, may result in deductions of decided value.

The effect of splenectomy in other diseases being the primary basis for the operation in pernicious anemia, the further indications must be mainly based on operative results, and as early results only are as yet available, such indications are presented with reservation and will undoubtedly be subject to further modification.

INDICATIONS FOR OPERATION

Size of Spleen.—It would appear that the larger the spleen the better the prospects that splenectomy will prove of benefit. It may be assumed in this disease that oversize means overactivity, and it has certainly been true, in our own experience, that the most consistently promising results following splenectomy have occurred when the spleen showed the greatest enlargement. However, good immediate results have been obtained also when little or no enlargement was present. The palpability of the spleen, therefore, has been looked on as one of the first considerations in discussing the advisability of splenectomy. Exclusive of three cases in which the spleens were very large, the spleens in a series of thirty-seven of our cases averaged 400 gm., as compared with the normal of about 195 gm. It should be remembered that any estimation of the size of the spleen before it has become actually palpable is rather speculative. W. J. Mayo early pointed out that frequently in exploring the spleen in the course of abdominal operations, and comparing its actual size with that noted in the clinical records, it is found that clinical records are not consistently correct and as a rule are accurate only when the organ is palpable.

Icteric Types of the Disease.—The very intimate relationship between the spleen and the acholuric icterus as seen in pernicious anemia, hemolytic jaundice and in hypertrophic cirrhosis is proved both by operative results and experimental studies. The remarkably rapid, complete and permanent disappearance of the jaundice in hemolytic jaundice, for example, following splenectomy is sufficient evidence of the splenic factor. Experimentally, it is very difficult to produce toxic jaundice in spleenless dogs by those poisons which readily produce it in the normal dog. In spleenless dogs under the administration of such poisons (particularly toluylendiamin) the bile remains thin and green, while in nonsplenectomized dogs it becomes viscid. Stadelmann was the first to attribute such acholuric jaundice to this thickening of the bile, which delays, by very reason of its viscosity, its own passage through the finer bile capillaries. A marked icteric discoloration in the skin in pernicious anemia may be taken as an indication that the spleen is to a large degree responsible for the abnormal blood destruction feature in the disease.

Response to Transfusion.—The transfusion of blood, particularly of small quantities at frequent intervals, has for some time been recognized as valuable treatment, though only of temporary character, in pernicious anemia. It has recently become evident, however, that transfusion is not only an excellent therapeutic expedient, but that in the immediate response following the procedure, it is of distinct prognostic value in foretelling the probable results of splenectomy. Definite improvement after transfusion is a strong indication for splenectomy, but when no benefit occurs from repeated transfusions, splenectomy will probably also prove futile, though the reverse of both these indications is occasionally true. Transfusion seems to serve a double purpose, as does the ligation of the blood supply in exophthalmic goiter, by

(1) improving the condition of the patient, and by (2) predicting rather accurately the effect of the major operation on the disease.

Duration of the Disease.—Although in our own experience satisfactory results may be obtained when the disease has been of long standing, we believe the results are not as favorable as those in cases in which the disease has existed a short time.

Radical measures to interrupt the progress of the disease while it is yet in an early stage seem logical. Although there is little positive knowledge as to the reason for the permanent disability of the bone marrow, it is probable that it is constantly overstimulated in an effort to meet the abnormal demands made on it, and also suffering from the influence of the hemolytic agent or some other toxin.

In pernicious anemia, like exophthalmic goiter, the course of the disease tends to be interrupted by periods of comparatively good health and normal bodily functions. Each recurrence, however, further damages the organs which are affected by the toxin, and although with the interruption of the process in its early stages there may be complete restoration to health, sooner or later, regardless of the further course of the disease, permanent injury results.

The ability of man to develop other hematopoietic centers, when the normal source of the supply of blood corpuscles, the bone marrow, is under great stress, is well known. Such centers have been demonstrated in the spleen, the liver and lymph nodes. Whether in pernicious anemia the augmentation of the hematopoietic functions is simply compensatory by reason of the increased blood destruction of the disease, or whether the bone marrow, under the influence of some specific toxin, is primarily diseased, so that immature red cells are put into the circulation, is as yet problematic. It is more than possible that pernicious anemia could be cured in its inception, like cancer, if treated properly; when it is well established, a vicious circle is produced

and a permanently disabled hematopoietic system is added to the primary etiologic factor or factors. The question of permanent cure in pernicious anemia, therefore, may ultimately depend, not only on interrupting the progress of the disease by removing what appears to be the primary factor, but also to a greater extent on our ability to restore the bone marrow and other hematopoietic structures to their normal physiologic functions. It is to be hoped that earlier recognition of pernicious anemia will result in earlier splenectomy.

Activity of the Disease.—The activity of the disease is an important consideration in discussing the advisability of operation. Splenectomy should be undertaken with hesitation in acute stages of pernicious anemia and especially with a falling blood picture. The operation cannot at the present time be advocated when cord changes and other permanent pathologic processes mark the terminal stages of the disease. Moreover, as already suggested, if it is not possible to tide a patient over the critical periods by transfusion, splenectomy is contraindicated. Definite statements based on the qualitative blood picture cannot be made, but if the hemoglobin is under 25 per cent. and cannot be raised, operative treatment is of considerable risk and has doubtful results.

The extent of the disability of the patient must of course be carefully considered. If a patient with every evidence of the disease is able to carry on his usual occupation, splenectomy cannot be strongly advocated, yet these may be the very patients in whom good results may be obtained. The operation may be urged more legitimately when the patient is unable to do his work or is a chronic invalid.

A positive diagnosis of pernicious anemia having been made and the advisability of splenectomy established, it is important that the patient and his family be correctly informed as to the purpose and the status of splenectomy.

Splenectomy we have found of less technical difficulty in pernicious anemia than in any other disease or condition. An incision toward the outer edge of the left rectus extending above to about one inch from the costal margin and below to the level of the umbilicus is satisfactory. An abdominal exploration should first be made, especially in view of the frequent complications of liver and gallbladder met with in those diseases for which splenectomy is advocated.

The dislocation of the spleen from its position against the diaphragm and against the left kidney is not, as a rule, complicated by formidable adhesions in pernicious anemia; nevertheless, the operation is facilitated and the minor oozing points are controlled by the introduction of a large abdominal pack against the newly exposed surface. In the actual removal of the spleen it must always be borne in mind that the stomach and pancreas are in close anatomic relationship. The fundus of the stomach is in such immediate apposition to the gastric surface of the spleen that its wall may be injured if the gastrosplenic omentum at this point is not divided with particular care.

The tail of the pancreas does not bear a constant relationship to the splenic pedicle. In some instances it lies in front; in others behind, and it may extend along the pedicle until its tip rests in the hilus of the spleen. It is quite evident, in certain cases, that the tip of the pancreas must be dislodged from its position if the pedicle is to be ligated without injury, although such a condition is relatively unusual in pernicious anemia. The pedicle is rarely of sufficient size to present any difficulties in its control. It is comparatively easy to isolate the artery and the veins and ligate them independently. Although it has been advised that the artery should be ligated first in order that the spleen may empty itself of its blood, and although I have done this in some cases, I have never been able to observe any difference in the convalescence or the effect of

splenectomy on these patients, as compared with those in whom the artery and veins were ligated at the same time.

All bleeding points having been securely controlled, the pack is removed and the diaphragmatic surface inspected.

SUMMARY

We believe that splenectomy should be considered in every case of pernicious anemia in which the diagnosis has been established and all possible etiologic factors which might be independently remedied have been excluded. The failure of other means to combat the disease, the previous fatal prognosis, and the low operative mortality are strong arguments in favor of splenectomy. Contraindications must be positive and adequate. Granting this, however, we must be cautioned by our imperfect knowledge of the surgical indications. The conservative selection of cases is therefore advisable.

PERNICIOUS ANEMIA TREATED BY SPLENECTOMY AND SYSTEMATIC, OFTEN-REPEATED TRANSFUSION OF BLOOD

TRANSFUSION IN BENZOL POISONING *

ROY D. McCLURE, M.D.
DETROIT

Transfusion of blood in cases of pernicious anemia is perhaps the first remedy that suggests itself for the treatment of the malady. It probably was tried long before it is recorded in the literature. Since the newer ways of transfusion with syringes and the citrate method have so simplified the operation, it has been tried innumerable times, but with only indifferent success. The best it has accomplished has been to initiate a remission in the course of the disease. There are many reasons why these transfusions have not been of more value. Chief among these is the lack of systematic treatment. Usually about as much good is accomplished by a single transfusion as is accomplished by a single inunction of mercury in the treatment of syphilis. Discredit has also been incurred by using blood which has not stood the proper tests and which is not only unsuitable but is often positively harmful and which may result in disaster.

The practice of transfusion of blood since it was first performed in man in 1666 by Jeane Baptise Denys, professor of philosophy and mathematics in the Royal University in Paris and physician to Louis XIV, and by his teacher Dr. Lower[1] in London, who had developed the method by his work with his experi-

* From the Surgical Clinic of Dr. W. S. Halsted, Johns Hopkins Hospital.

1. Philosophical Transactions and Collections of Medical and Philogical Papers, John Lowthrop, 1731.

ments on animals in 1660, has passed through periods of great disrepute. At first it fell into disfavor because the blood of animals, dogs, sheep and calves was used and there were probably deaths from anaphylaxis. The road to safe transfusion was not made possible until Landois[2] in Greifswald in 1870 discovered that the blood of one man was not always compatible with the blood of others, though I believe he never explained it, yet he did show that the serum of one animal might dissolve the red blood cells of another animal. It remained for Moss[3] in this country and for Landsteiner[4] and Jansky[5] abroad to show that the blood from two individuals may not mix well, due to the following facts:

1. That the red corpuscles of one or of each may be clumped by the serum of the other.

2. That corpuscles clumped in this way may be hemolyzed as well.

3. That all human beings soon after birth may be grouped into four distinct classes, depending on the ability of their serum to agglutinate the red corpuscles of members of the other groups and on the susceptibility of their corpuscles to agglutination by the serum of members of the other groups.

In the selection of a donor little attention for a time was paid to the fact that the serum of an individual in one group hemolyzed and agglutinated the cells of a person in another group. Some men doing transfusions wrote as late as 1912 that the action of one blood on another was not necessarily the same in vitro as in vivo, and they rather scoffed at these tests. This attitude could only do harm to the reputation of transfusion as a therapeutic measure. I know that deaths have occurred as the result of transfusion when the tests were ignored or improperly performed. Even when the tests were properly performed and the bloods

2. Landois: Die Transfusion des Blutes, 1875.
3. Moss: Bull. Johns Hopkins Hosp., 1910, xxi, 63.
4. Landsteiner: Wien. klin. Wchnschr., 1901, xiv, 1132.
5. Jansky: Klin. sborn., 1907, No. 2; abstr., Jahresb. f. Neurol. u. Psychol., 1907.

reported compatible, we have had one case of severe hemolysis. On returning to the laboratory tests we found that agglutination was present at the end of one hour, but we had accepted the report as favorable at the end of a half hour. Therefore, we concluded that the report of compatibility can not be safely made under an hour.

In an extended series Moss has found that the relative frequency of the groups is as follows: Group 1, 8 per cent.; Group 2, 36 per cent.; Group 3, 9 per cent.; and Group 4, 47 per cent. Gorham and Lisser[6] found that the serums of the various groups differed in the rapidity with which they brought about agglutination of the corpuscles of the other groups. Thus Group 4 required five minutes or less, Group 2 often fifteen minutes to half an hour, and Group 3 still longer for positive identification.

The selection of a proper donor is therefore a very important matter, and often rather difficult if the patient belongs in one of the rarer groups, 1 or 3. It is also imperative that transmissible diseases be ruled out by history, blood examination, Wassermann, etc. I wish to report here for the first time the transmission of syphilis by transfusion in a case of pernicious anemia. The donor was a close relative of the patient and before giving his blood denied having syphilis and also denied exposure to infection. Less than six weeks after this transfusion the patient returned with the most virulent syphilitic rash and mucous ulcers. At the same time the secondary eruption appeared in the donor. It then developed that the donor had a primary sore at the time he gave the blood. Malaria was transferred in one of the early cases by a transfusion of defibrinated blood. It was in the quiescent stage in the donor, but flared up in the recipient.

Transfusion has usually been carried on in cases of pernicious anemia in a very desultory or sporadic fashion, and as we have pointed out, often without

6. Gorham and Lisser: Am. Jour. Med. Sc., 1912, cxliv, 103.

proper donor being selected, consequently it was soon regarded as of little value in this disease.

Our attention was first drawn to the great value of repeated transfusions, in 1914, in the treatment of benzol poisoning.

On the service of Dr. L. F. Barker at Johns Hopkins Hospital in 1909 there were admitted the first of a series of cases of benzol poisoning. The patients were girls employed in a canning factory in Baltimore. Benzol (benzene, C_6H_6) was used in dissolving rubber and the fumes resulted in the poisoning of the workers. The symptoms are a severe purpura hemorrhagica with a severe anemia of the aplastic type. Several transfusions were performed among these cases, but as there was only temporary improvement, if any, the procedure was regarded as of little value. Several patients died soon after admission. The following case we report, as the result of each transfusion was so striking, one of the operations so plainly saving her from immediate death. Our previous results had been so discouraging, as the improvement of a single transfusion was so temporary, and we were ready to give up. The family of the patient, however, saw the enormous immediate benefit of each transfusion and insisted that we continue with this treatment. They produced the donors, so we always had suitable blood. Much to the surprise of all of us she soon ceased to require transfusion and made a complete recovery.

S. H., a woman, aged 31 years, worker in a canning factory, admitted to the hospital May 1, 1914, complained of bleeding from the nose and mouth. A diagnosis of benzol poisoning and secondary anemia was made. Her family history was unimportant. Her present illness began with an onset seven weeks before entrance (early part of April, 1914), with a feeling of weakness and bleeding from the nose. The hemorrhage usually lasted from one-half to two hours. Black and blue spots appeared over the body, followed by shortness of breath, bleeding from the gums and loss of appetite.

On examination the woman was found to be pale and obese. There was bleeding from the margins of the gums. There was no general glandular enlargement. The lungs were clear, the heart slightly enlarged. A systolic blow was perceptible

at the base. Numerous purpuric spots were distributed over the body, and there was slight edema of the extremities.

On May 2, 1914, the red blood cell count was 1,460,000; white blood cell, 1,110; hemoglobin 25 per cent.; polymorphonuclears, 40 per cent.; mononuclears, 37 per cent.; transitionals, 15 per cent.; no nucleated red blood cells; no myelocytes. Platelets were almost absent. Bleeding time fourteen and one-half minutes; normal time is one-half to two minutes.

Transfusions were done by the Carrel end-to-end method. The results are shown in Table 1.

After each of the first three transfusions she rapidly lost what she had gained and unfortunately another transfusion was not done until she had slipped back. The fourth transfusion was all but too late. A massive transfusion was done, probably 1,500 c.c. or more of blood being given, and there was a great rise in hemoglobin. (We were still using the end-to-end suture method, so no measurement of the quantity of blood could be made.) Normoblasts and nucleated red cells made

TABLE 1.—RESULTS OF TRANSFUSIONS IN CASE OF SECONDARY ANEMIA FROM BENZOL POISONING (SUTURE METHOD)

No.	Date, 1914	Hemoglobin, per Cent.			Red Blood Cells		
		Before	After	Increase	Before	After	Increase
1	5/ 8	20	38	18	1,226,000	1,680,000	454,000
2*	5/17	28	48	20	1,117,000	1,971,000	864,000
3	5/23	20	40	20	910,000	1,856,000	946,000
4†	5/31	11	42	31	0	0	
5	6/13	48	65	17	3,476,000	4,528,000	1,052,000

* Defibrinated blood.
† Patient bleeding, comatose.

their appearance and after the next transfusion (donor a negro man) the patient made an uneventful recovery, and was discharged from the hospital July 26, 1914.

Jan. 17, 1916, the patient has remained well, the hemoglobin being 95 per cent.; red blood cells, 4,272,000.

This led us to believe that perhaps steady use of carefully planned transfusions persistently used to prevent the anemia and its results might be of benefit in pernicious anemia. We advocate, too, splenectomy.

Since Eppinger in May, 1913, first called attention to the very beneficial effect of splenectomy in pernicious anemia, it has been widely performed. American surgeons have reported often great improvement, but probably no cure. It is unnecessary to discuss it further after the papers of this symposium. Eppinger

regards splenectomy as the most important measure in the treatment of pernicious anemia.

Table 2 shows a brief résumé of our transfusions in pernicious anemia. As will be seen, splenectomy was carried out in only six of these cases, three by Dr. Finney and three by myself.

TABLE 2.—RESULT OF TRANSFUSIONS IN SEVENTEEN CASES OF PERNICIOUS ANEMIA, SIXTY-FOUR TRANSFUSIONS BEING MADE WITH NO DEATHS *

Result	Number	Per Cent.
Beneficial	34	53
No benefit	23	35
Harmful	7	10
Severe reactions	7	10
Slight reactions	12	19
Chill	7	10
Dilated heart 24 hr. after transfusion	1	1½
Jaundiced	1	1½
Hemoglobinuria	3	4½
Temp. elevation over 101	12	19
Skin eruptions	7	10

* Splenectomy was performed in six cases.

The transfusions that resulted harmfully or were of no benefit we feel due to improper matching of the blood. This resulted in still greater care in the selection of donors. In the earlier cases, little benefit resulted from the fact that only a single transfusion was done. We will report only three cases here as there is not space for all.

CASE 1.—T. A., aged 38, was admitted to the hospital Feb. 22, 1915, complaining of progressive weakness. A diagnosis of pernicious anemia and pyorrhea alveolaris was made. The family and personal history were unimportant. The present illness had its onset in June, 1914, with weakness, followed by loss of appetite, constipation, nausea and vomiting, and a loss of weight of 24 pounds. There was dyspnea but no nervous system symptoms.

Blood examination made Feb. 22, 1915, showed red blood cells, 1,584,000; white blood cells, 4,560; hemoglobin, 32 per cent. The color index was high; the differential count, 70 per cent., polymorphonuclears, mononuclears, 25 per cent., 1 nucleated red blood cell.

On Jan. 17, 1916, blood examination showed hemoglobin 93 per cent.; red blood cells 3,728,000; polymor-

phonuclears 77 per cent.; small mononuclears 10 per cent.

CASE 2.—J. B., a woman, aged 43, was admitted to the hospital, Sept. 10, 1915, complaining of weakness, shortness of breath, and pallor. A diagnosis of pernicious anemia was made. The family history was negative. The personal history of the patient showed that the bowels were regular, and that she had had two miscarriages. Otherwise the history was unimportant.

The patient had had cystitis for two years, appetite poor, with a burning sensation of tongue and mouth. The temperature was from 99 to 101. There had been some dizziness for six months. A roaring sensation in ears had been noticed for two months. There was slight edema.

TABLE 8.—EFFECT OF TRANSFUSIONS ON THE PATIENT T. A., CASE 1

No.	Date, 1915	Amt. C.c.	Hemoglobin, per Cent.			Red Blood Cells		
			Before	After	Change	Before	After	Change
1	8/ 9	700	25	33	8	1,428,000	1,920,000	492,000
2	8/26	750	54	67	13	2,128,000	2,440 000	312,000
3	7/ 8	650	29	40	11	840,000	1,656,000	816,000
4	7/10	675	32	41	9	1,296,000	2,128,000	832,000
5*	7/24	700	35	?	?	1,884,000*	?	?
6	8/ 8	700	29	45	16	?	?	?
7	8/27	700	40	60	20	1,888,000	3,220.000	1,332,000
8	9/ 1	652	50	60	10	1,960,000	3,088,000	1,128,000
9	9/ 8	675	60	70	10	3,088,000	3,144,000	56,000
10	9/ 9	675	60	65	5	2,424,000	?	?
11	9/11	680	65	75	10	2,424,000	3,688,000	1,264,000
12	9/23	770	80	85	5	3,632,000	4,432,000	800,000
13	10/ 7	675	80	90	10	4,928,000	5,280,000	352,000

* Splenectomy was performed following fifth transfusion.

On examination of the patient the mucous membranes were found pale; the blood pressure was 150 mm. of mercury systolic, 80 diastolic; the temperature was 100.4. There was an impaired percussion note at the apexes of the lungs, but no râles. The heart was slightly enlarged. A systolic murmur was heard at the apex. The liver was not enlarged and the spleen could not be felt. There was no general glandular enlargement. The reflexes were normal. The stools were negative.

Blood examination showed hemoglobin 27 per cent.; red blood cells 1,136,000; white blood cells 3,560; polymorphonuclears, 66 per cent.; eosinophils, 0.5 per cent.; basophils, 0.5 per cent.; small mononuclears, 27.5 per cent.; large mononuclears, 3 per cent.; transitionals, 1 per cent.; myelocytes, 1 per cent.; myeloblasts, 0.5 per cent.

On September 12 the hemoglobin was 29 per cent.; white blood cells, 2,000; red blood cells, 944,000. There were fresh

hemorrhages in both eye grounds. The Wassermann was negative. Gastric analysis showed hydrochloric acid deficit 8 per cent.; total hydrochloric acid 2 per cent.

CASE 3.—H. P., a widow, white, aged 62, was admitted to the hospital Jan. 3, 1916, complaining of weakness and lack of blood. Her family and personal history were unimportant. Previous to her present illness she had always been healthy and strong. The onset occurred in January, 1914. There was increased frequency of urination. A few weeks later there was weakness of the knees, progressive shortness of breath, and for three weeks, pain over the heart. There had been no fainting or giddy spells; she had lost 37½ pounds in weight.

Examination showed a woman of large frame, with dyspnea on slight exertion. There was a lemon color to the skin, and evidence of recent loss of weight; no general glandular enlargement; teeth practically all gone; chest symmetrical;

TABLE 4.—EFFECT OF TRANSFUSIONS ON THE PATIENT J. B., CASE 2

No.	Date, 1915-16	Amt. C.c.	Hemoglobin, per Cent.			Red Blood Cells		
			Before	After	Change	Before	After	Change
1	9/25	800	20	35	15	680,000	1,520,000	840,000
2	9/30	900	35	45	10	1,664,000	2,048,000	384,000
3	10/ 9	900	55	76	21	2,240,000	3,520,000	1,280,000
4	10/16	900	76	85	9	2,432,000	4,176,000	1,744,000
5	10/24	20	85	52	33*	4,176,000	2,672,000	1,504,000*
6	10/30	900	47	62	15	3,624,000	4,000,000	376,000
7	12/11	788	22	40	18	648,000	2,158,000	1,510,000
8	12/14	900	42	55	13	2,450,000	3,158,000	708,000
9	12/18	800	?	?	?	?	?	?
10	12/21	280	..	48	..	.....	3,000,000	
11	12/30	550	53	48	5*	1,900,000	?	?
12	1/22	500	51	70	19	3,368,000	3,648,000	280,000
13	1/12	660	74	78	4	3,792,000	?	?
14	1/14	270	78	82	4	?	?	?

* Lost, due to hemolysis.

costal angle almost straight. No râles; region of cardiac dulness extended 4.5 cm. to the right and 11 cm. to the left of the midline. There was a systolic murmur at the base of the heart and a diastolic murmur over the vessels of the neck. The blood pressure was 118 mm. of mercury systolic, 60 diastolic. The liver was not enlarged, and the spleen could not be felt. The reflexes were difficult to obtain. There were no sensory disturbances. Rectal examination was negative. Red blood cells were 936,000; white blood cells, 5,440; hemoglobin 26 per cent.; polymorphonuclears 50 per cent.; eosinophils, 0.4 per cent.; basophils, 0.4 per cent.; small mononuclears, 28.8 per cent.; large mononuclears, 2.8 per cent.; transitionals 0.8 per cent.; myelocytes 13.6 per cent.; unclassified, 3.2 per cent.; red blood cells January 7, 1,088,000; hemoglobin 25 per cent.; Gastric analysis showed no free hydrochlorates; stool examination was negative; eye grounds normal except for pallor of

the disks. January 10, red blood cells 1,288,000; hemoglobin 23 per cent.

The repeated systematic transfusion has been carried out only during the past year. The results, however, have been so encouraging that we feel that the life of a patient with pernicious anemia may be indefinitely prolonged if the spleen is removed as soon as the patient is in condition to stand the operation, and sometimes we have to transfuse several times before splenectomy.

TABLE 5.—EFFECT OF TRANSFUSIONS ON THE PATIENT H. P., CASE 8

No.	Date, 1916	Amt. C.c.	Hemoglobin, per Cent.			Red Blood Cells		
			Before	After	Change	Before	After	Change
					Loss			
1	1/12	200	26	23	3	1,224,000	1,440,000	216,000
2	1/21	300	21	26	5	1,440,000	1,448,000	8,000
3	1/24	682	29	36	7	2,352,000	2,608,000	256,000
4	1/26	640	36	50	14	2,352,000	2,416,000	64,000
5	2/ 2	630	50	55	5	2,416,000	2,434,000	18,000
6	2/ 7	660	54	65	11	3,040,000	4,680,000	1,640,000
7	2/19*	450	65	?	?	2,482,000	2,726,000	244,000
8	2/26	360	68	?	?	3,072,000	?	?
9	3/ 6	500	70	76	6	3,752,000	3,824,000	72,000
10	3/13	450	71	86	15	3,584,000	4,736,000	1,152,000

* Splenectomy was performed February 12.

After the spleen is removed if there is not a rapid improvement in the blood picture, we would advocate transfusion until the hemoglobin is as high as 90 per cent. or more, never allowing it to fall below 75 per cent. As remissions often last several months or a year, not many transfusions may be required. It is well known that anemia so reduces the resistance of the body to infections that it is often an easy prey. Thus can the usual secondary causes of death in pernicious anemia be avoided, and who can tell but that within a few years of persistent transfusions the primary cause, whatever it may be, of pernicious anemia may lose its force and perhaps the disease be cured.

I wish to thank Dr. George R. Dunn for his assistance in preparing the abstracts and tables for this article.

Henry Ford Hospital.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. LEE, MINOT AND VINCENT, KRUMBHAAR, MILLER, PECK, BALFOUR AND MC CLURE

DR. FRANK SMITHIES, Chicago: During the past two and a half years in the clinics of Drs. Percy and Ochsner we have treated twenty-seven cases of pernicious anemia by multiple transfusion of whole blood and splenectomy. Our cases have strongly impressed on us the value of the observations of William Hunter with respect to the toxic or even the infectious nature of the ailment. Just what effect on the hematopoietic tissues may be produced by a periodically recurring low grade infection it is not at present possible to fully state. Of peculiar significance, in my opinion, is the fact that in practically all of our cases, infective foci were demonstrable. The removed spleen showed evidences of chronic splenitis and perisplenitis, indicating that a toxic or infective process had been chronically going on. It has not been possible to culture organisms from the blood or the tissues. It would seem that work similar to that which Rosenow has carried out in tissue culture will at some time demonstrate organisms which at present escape detection. The term "treatment by splenectomy" is, I think, misleading and incomplete. The splenectomy is merely one part of the treatment and frequently a part of the treatment which may perhaps later on be proved to be the least essential. The routine of treatment which we have emphasized is: multiple, massive transfusions of whole blood, eradication of local foci of infection wherever such may exist, and lastly, laparotomy for removal of the spleen and other tissues evidencing chronic subinfection.

Multiple blood transfusions supply protective antibodies and enable the patient to get rid of the secondary changes which have been going on in the various organs. They improve the blood in quantity and quality. They thus bring the patient to his splenectomy as a fair to good operative risk. During the multiple blood transfusion the patient can be treated with regard to self-evident infection. The operative procedure then becomes relatively safe. Of the twenty-seven cases operated on by Dr. Percy there were but two operative deaths, and one other death within three months following splenectomy. I attribute this rather remarkable experience to the fact that the patients were carefully prepared for the major operation. I attribute many of the poor results following splenectomy in pernicious anemia to the patient's being rushed into splenectomy before he has been properly prepared as a surgical risk. Ninety per cent. of the cases which I observed showed subinfections in the gall-bladder or appendix and all showed evidences of chronic infection in the spleen.

The effects on the blood in the cases I have studied are: In cases that have run from four to twenty-seven months following our treatment there has been an average hemo-

globin gain of 43 per cent.; an average gain of red cells of 3,322,000, and this gain has in general been well maintained. Study of blood smears shows an absence or diminution of nucleated red blood cells of 94 per cent. There was a decrease in the color index in 68 per cent. There was a permanent increase in the leukocytes in 88 per cent.; a decrease in coagulation time in 66 per cent.; a decrease in polychromatophilia in 56 per cent., and the establishment of a relative polymorphonuclear leukocytosis in 61 per cent.; a reduction, relatively, in lymphocytosis in 55 per cent., and a definitely demonstrable gain in blood platelets in 61 per cent. Patients frequently improved, clinically, out of all proportion to the apparent improvement in the blood picture. The permanence of these results no one can at present state. One patient treated twenty-seven months ago is in most excellent shape after having been a useless invalid for more than two years previously.

Dr. Beth Vincent, Boston: Transfusion is so often combined with splenectomy in the treatment of pernicious anemia that they may be considered together in discussing the effects of splenectomy. At the Massachusetts General Hospital we always test donor and recipient before transfusion in pernicious anemia and use as donor a person of the same blood group as the recipient. We transfuse on an average of 600 c.c. of blood in these cases and believe that a relapse which does not show a tendency to spontaneous remission is an indication for transfusion. Some of our patients were transfused before splenectomy and others received transfusions afterward in the relapses which eventually occur in these cases. Dr. Minot has called attention to the increased activity of the bone marrow which follows splenectomy and is shown by the appearance of Howell-Jolly bodies, a rise in the leukocyte count and an increase in the blood platelets and reticulated reds. A similar change may be observed after transfusion and appears on the fourth to tenth day. This furnishes the most favorable time to do a splenectomy in these cases which have been transfused in preparation for the operation. The mortality of splenectomy in pernicious anemia should be very low, provided the right stage of the disease is taken to do the operation. I feel that it is a mistake to remove the spleen in a relapse. Such a case should be transfused and not operated on until it has reached the stage of improvement. There is a type of pernicious anemia, one whose course is steadily downward without remissions which does not improve with transfusion and, in our experience, this type of case shows very little change after splenectomy. As to results, the figures in our series of 15 cases agree with those given by Dr. Krumbhaar. The immediate effects of splenectomy are often strikingly favorable, but the longer the cases are followed the less encouraging they become.

Splenectomy is capable of bringing about a satisfactory remission of considerable duration. It may last six months and rarely lasts a year. After this period the disease resumes its normal course. Removal of the spleen does not prevent the recurrence of relapses or alter their severity. I doubt whether it prolongs the patient's life unless the case is followed to the end and transfused in the relapses. Transfusion is undoubtedly the best treatment for a relapse. It does not give such a permanent result as splenectomy but makes the patient more comfortable and probably prolongs his life. Therefore splenectomy and transfusion are palliative, not curative. Splenectomy diminishes blood destruction and both splenectomy and transfusion are followed by bone marrow activity which brings about a temporary symptomatic improvement. This benefit is temporary and not always certain but nevertheless transfusion and splenectomy are the most effective means we have at the present time for the treatment of pernicious anemia.

DR. HERBERT ZIEGLER GIFFIN, Rochester, Minn.: This symposium is very important at this time because it crystallizes our ideas in regard to the present status of splenectomy for pernicious anemia. I can only add our own experience to that which has been given. It is almost exactly in line with the results that have been reported. Thirty-nine cases have been operated on with an operative mortality of 3 (7.7 per cent.). There is apparently no reason why the operative mortality for pernicious anemia should be high. There have been four postoperative deaths, leaving thirty-two living patients. Five patients are at present in relapses, so of thirty-nine cases there are twenty-seven patients in good or fairly good condition. One patient lived as long as three years. The longest period during which patients have maintained a good condition is one year, which occurred in two instances. Preoperative transfusions have been given preparatory to operation to improve the general condition of the patient, to initiate if possible an upward wave and to improve the characteristics of the blood count. One can predict that four patients out of five will show a very marked gain after splenectomy and it would seem that they should be given the opportunity to have this gain without very strenuous postoperative treatment. We have given postoperative transfusions only in relapses. I wish to speak here especially of the examination of the duodenal contents of pernicious anemia patients for the blood derived pigments. We have followed up the work of Schneider reported in January in the *Archives of Internal Medicine* in thirty-three cases of pernicious anemia and have obtained high values for urobilin and urobilinogen in the duodenal contents by the Wilbur and Addis spectroscopic test in all but three. In 12 cases examined a short time after splenectomy ten gave very

low value. We have examined the duodenal contents for blood derived pigments in nineteen cases of a miscellaneous group with secondary anemia and have obtained low values. In four cases of hemolytic jaundice three have shown high values. This test may prove to be important in the study of patients with pernicious anemia. For instance, if a patient shows high hemolytic values in the duodenal contents and is able, in spite of active hemolysis, to maintain a good blood picture, he should be a favorable case for splenectomy: for splenectomy is followed by a reduction of the hemolytic values. With splenic anemia our experience is of thirty-three cases. The results are uniformly good. With hemolytic jaundice our experience is of ten cases with one death. In hemolytic jaundice there has been a very great improvement in the general condition of the patient, the jaundice and the anemia. We have one patient in excellent condition who was operated on eight years ago. One case of acquired hemolytic jaundice presented a pernicious anemia blood count. Cases of hemolytic jaundice in adults which show a pernicious anemia type of blood count are particularly interesting because of a possible close relationship between the two diseases.

DR. W. S. THAYER, Baltimore: My first experience in which I had a splenectomy done in pernicious anemia dates from three years ago next November. That patient had already had distinct signs of spastic paraplegia. She made what appeared to be a complete recovery from the standpoint of her anemia and remained well for a year and a half. Her cord changes failed to progress. Then, in about two or three months, she rapidly went down hill with a relapse and died from a characteristic pernicious anemia. I felt that while we had only succeeded in producing a remission of the anemia that we had for the first time in my experience done something which arrested the progress of the cord changes and yet Dr. Krumbhaar is able to tell us that, as a rule, the cord changes have progressed without respect to the operation. Dr. Miller had an instance almost opposite to mine, that is, the anemia improved, but the cord changes grew rapidly worse. With splenectomy there is a temporary improvement in the majority of instances. The best figures show a considerable mortality from the operation. One is tempted to regard pernicious anemia as inevitably fatal and one is justified in seeking any remedy which may bring improvement. There are cases of long remissions—McPhedran's of sixteen years; others of shorter time. I myself saw one of five years and the patient died of another malady. We never need be utterly hopeless with regard to pernicious anemia and one must consider very carefully before advising splenectomy. We do in most cases accomplish a little something which we may not be able to accomplish under other circumstances, but it ought to be

put very directly to the patient and it seems to me we should go very slowly in advising so serious a procedure. In regard to splenic anemia, particularly those with violent gastric hemorrhages, the results did not seem to be uniformly beneficial. My experience has been quite in accord with that of the other gentlemen who have spoken. In hemorrhagic jaundice the results appear to be almost uniformly beneficial, but there again one ought to consider very seriously the question of operation before advising definitely to have it done. If we are dealing with a case of congenital hemolytic jaundice, as a rule, the symptoms are not grave. I have three cases now under observation, in all of which the patient does not suffer much. There is a large spleen and a continued jaundice of greater or less degree quite endurable, so endurable that in none have I felt like advising splenectomy. One of these patients who underwent appendicitis associated with the removal of stone from the gallbladder withstood the operation as well as a healthy person and, indeed, three weeks after the operation the fragility of the blood was less than it was before. One should not urge an operation. The jaundice may be so serious and the anemia grave enough to justify it. In instances of acquired hemolytic jaundice it may be that the anemia is serious enough to make the operation almost imperative. These methods of transfusion have rendered the possibility of doing splenectomy in grave anemia a relatively simple matter where previously it would have been absolutely impossible. I remember an instance of splenic anemia, operated on by Dr. Finney, in a small boy, where he had waited six months that he might develop a good color. Finally, the boy's condition became so serious that he was transfused and taken to the operating room practically moribund and transfusion was done while operation was being carried out. By the end of the operation the arteries were spurting and the boy made a perfect recovery following the operation.

DR. G. A. FRIEDMAN, New York: I shall limit my remarks to hemolytic jaundice. It is the third case of Dr. Peck to which I refer. The patient stated that he was sick for eight months and on close questioning, no other illness could be elicited, except that when he was very young he had a fever which lasted for several days. There was undoubtedly no hereditary tendency in this case. When first seen, I would say that he was more icteric than sick, and, practically, he came to the clinic, not so much for his symptoms, as for his jaundice. One of my co-workers on first examination suggested catarrhal jaundice. It is very important, and especially so in cases of young people, that the first thought that should come to the mind should be catarrhal jaundice. But an icterus which begins acutely with enlargement of the spleen should suggest hemolytic jaundice. We know well, however, that in a proportion of cases of catarrhal jaundice

the spleen is enlarged and not the liver. But on considering more carefully the history in the case at hand, one must see that we are dealing with an entirely different condition. There was an absence of pruritus during the entire period of the illness — eight months. The absence of bile in the urine, and the presence of urobilin and urobilinogen, the presence of bilirubin in the blood, and the presence of bile in the stools, are aids in the diagnosis. The anemia here, however, was not marked. The resistance of the red blood cells to hypertonic salt solutions was only slightly diminished. It was between 0.35 to 0.45, but the percentage of the reticulated red cells was increased. The result of the operation was marked. Patient was practically free from jaundice on the fourth day after the splenectomy and on the eighth day there was no trace of it. I saw him at the end of last March. There was no jaundice and the patient was well. The medical treatment is absolutely without any benefit.

DR. SAMUEL J. MELTZER, New York: I wish to point to a possible factor which, as far as I know, has not been referred to either in the experimental or in the clinical work on the subject. We know that the red corpuscles run in the middle of the blood stream and are, therefore, as a rule, not exposed to any kind of shocks. Some forty years ago I saw a fragile red corpuscle riding on the ridge formed by two dividing arteries. The blood cell was finally broken into two fragments. It then occurred to me that the blood corpuscles while passing through the spleen must be subject to innumerable shocks. The blood, after leaving the renal artery, passes through a considerable amount of alveolar tissue, before it enters into the renal veins. The blood cells in their rapid run through these tissues must continually come in conflict with some jarring ridges. This gave me the notion that fragile red blood corpuscles may readily break down in the spleen or may be prepared to give up some of the hemoglobin, and that some of the nucleated cells may lose their nucleus there. I was also thinking that the mechanical shocks which the white corpuscles receive while passing through the irregular arrangement of the alveolar tissue may be affected; it may possibly hasten their natural division. These considerations were the starting point for many of the investigations on the effect of shaking on red cells, bacteria, ferments and toxins. The first investigation of this kind was carried out in 1884, together with Dr. Welch. In the course of the last year Dr. F. L. Gates studied in our laboratory at the Rockefeller Institute the effect of shaking on red cells of splenectomized dogs. I am not ready to report here his results. I merely wish to call the attention of those who are interested in this subject that the mechanical effect of the alveolar construction of the spleen may have a certain influence on the red blood corpuscles, at least

in pathologic conditions of the blood, and may be, therefore, a potent factor in certain forms of anemias.

Dr. Roger I. Lee, Cambridge, Mass.: The ordinary course of pernicious anemia is very bizarre, although it is next to impossible to tell from a few cases whether the effect of a particular therapeutic agent is favorable or not. The blood picture in pernicious anemia may be said to correspond roughly to blood destruction and blood formation. The same thing holds true of hemolytic jaundice and splenic anemia. We have studied splenectomy and transfusion from the point of view of the effect of stimulating the bone marrow activity by the method that Dr. Minot outlined. We have used no particular method, but we have used those general comprehensive estimates of all these methods. We do not think, for example, that the reticulate cells alone are of very great value, but the qualitative changes in the reticulate cells, especially with the blood platelets and white corpuscles, give us good information in regard to the bone marrow. After splenectomy and after transfusion we always get a slight tendency toward stimulation of the bone marrow. That stimulation of the bone marrow varies a great deal. It is much more constant. It is much more constant and energetic after splenectomy than after any other therapeutic procedure. The benefit of transfusion is to furnish bulk of blood which may then be destroyed very rapidly, but the main benefit of transfusion is to inaugurate a remission which means merely to stimulate the bone marrow and it is only by following the patients that we can tell whether they are benefited or not. We merely say that after splenectomy rather constantly and after transfusion occasionally one does see the signs of a stimulated bone marrow.

Dr. E. B. Krumbhaar, Philadelphia: It has been generally accepted not only that blood transfusions are a valuable prelude to splenectomy, but that in themselves they constitute an efficient method of combating pernicious anemia. In fact it remains to be proved whether or not equally good results would not be obtained by repeated transfusions in the absence of splenectomy, although the impression is prevalent that the improvement following splenectomy is more lasting. This is to be expected if it is borne in mind that whereas transfusion merely improves the condition of the blood, splenectomy removes the most apparent noxa. In connection with Dr. Thayer's remarks about the long periods of spontaneous remissions, I would call attention to Cabot's series of 1,200 cases in which only three patients were considered as "cured," in other words, did not develop symptoms during five years. May it not be that among the small number of splenectomized patients that we have thus far had opportunity to see, there is a group which will eventually give us a larger proportion of long surviving cases?

I hesitate to use the word "cure," because we do not think of any of them as really cured. In regard to the use of the term "splenic anemia," I think most physicians would agree with Dr. Miller that it probably includes one or more clinical conditions of uncertain or varying etiology. But just as the hemolytic jaundices, and probably also von Taksch's disease have been separated from this group with profit, so also Gaucher's splenomegaly, with its unique pathology and well-defined symptom complex, should to my mind be considered an independent condition. Thus "splenic anemia" in the present state of our knowledge might profitably and feasibly either be discarded entirely, or considered as synonymous with Banti's disease, or with the two early stages of that disease.

DR. JOSEPH L. MILLER, Chicago: Not every patient with hemolytic icterus is inconvenienced by it. In fact, the majority of these patients suffer little or no inconvenience aside from discoloration of the skin. For this reason, Türck has referred to it as a cosmetic disturbance rather than a disease. It would seem, therefore, a question whether an operation with a mortality of at least 10 per cent. should be undertaken in these cases of hemolytic icterus, unless the person shows a definite disturbance or unless he should be willing to undertake the risk associated with the operation in order to be relieved of the icterus. There has recently been a report of three cases of hemolytic icterus cured, the result of Roentgen-ray treatment. In those cases in which splenectomy is not undertaken it might be well to try the effect of the Roentgen ray to see whether a cure might be effected.

PREMATURE VENTRICULAR SYSTOLES

THEIR CHEMICAL SIGNIFICANCE

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In presenting a number of polygraphic and electrocardiographic tracings to illustrate the subject of this paper, I shall endeavor to bring before you certain first principles in the recognition and treatment of this form of heart irregularity. While it is desirable that, from the standpoint of the clinician, graphic tracing should be made when practicable, nevertheless, we are able to distinguish such abnormalities in the heart action by careful palpation of the pulse and auscultation of the heart sounds.

It may be safe to say that in general, premature contractions of the ventricle have given rise to too many unfavorable prognoses, and it is equally apparent that the subject of premature ventricular systoles has not been given the proper attention from the standpoint of therapy.

As a matter of fact, the point of primary importance and a point which I desire to emphasize from the very start is this, viz., that the irregularity of the heart action to which I wish to call attention has too often been attributed to disease of the heart itself, whereas the real seat of trouble is usually extrinsic to the heart. In fact, I wish most emphatically to state that in a great majority of instances premature ventricular systole—meaning a too early contraction of the lower chamber of the heart—is a functional disturbance.

Premature ventricular systoles may be of very short duration; they may last for a somewhat longer time and finally disappear altogether; or they may be more

or less constant. They may be found in connection with hearts that show absolutely no other sign of disturbance, and they may be encountered in cases in which there is manifest organic disease of the heart. Even in the latter case, the premature ventricular discharge may not be the result of the organic lesion, but may again be the expression of a toxic condition in which the heart muscle becomes oversensitive.

Just as a patient with brain tumor may show signs of hysteria to complicate the clinical picture, so also may we have organic disease of the heart with certain functional disturbances, which are not essentially of cardiac origin.

THE RECOGNITION OF PREMATURE VENTRICULAR SYSTOLES

As a rule, the recognition of premature ventricular systoles is a matter of no great difficulty. In the majority of cases auscultation of the heart will prevent errors in diagnosis, since these premature contractions of the lower chamber of the heart usually give rise to a very characteristic sequence of heart sounds.

A glance at Figure 1 will demonstrate a number of factors which will serve to illustrate points in the diagnosis. The first five beats are regular in their sequence and they are the result of stimulation from the sinus node. The auricular contractions are regular, as may be seen by a glance at the chart. The *sixth* contraction of the ventricle is premature. It is in advance of the normal stimulus coming from above and, because the ventricle is in a refractory state when the sixth auricular stimulus arrives, the lower chamber is unable to respond to this command. The ventricle, therefore, rests for a longer period than usual, and does not contract or does not become active until the seventh stimulus arrives. This long pause is referred to as the compensatory pause. At the seventh stimulus the heart again contracts normally and this seventh normal beat is then seen to be followed by another premature con-
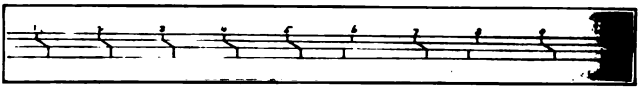
Fig. 1.—Diagram to illustrate premature contractions of the ventricle.

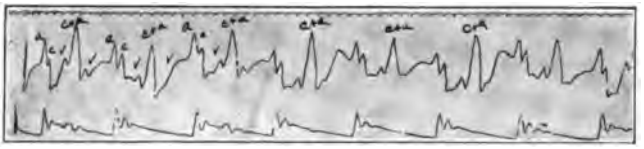

Fig. 2.—Bigeminal pulse, in which every second beat is a premature ventricular systole.

Fig. 3.—Premature contractions arising in the left ventricle.

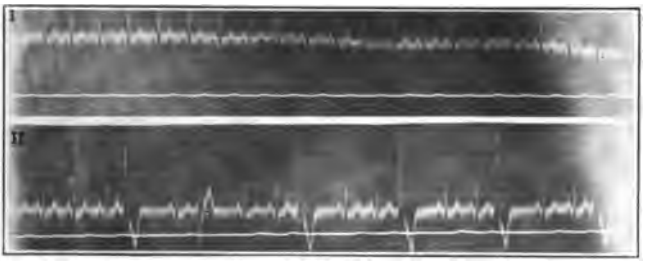

Fig. 4.—Two tracings from the same patient; upper tracing, Lead I; lower tracing, Lead II.

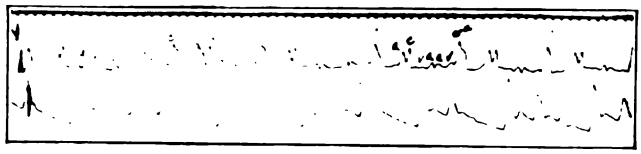

Fig. 5.—Marked irregularity due to frequent premature ventricular contractions.

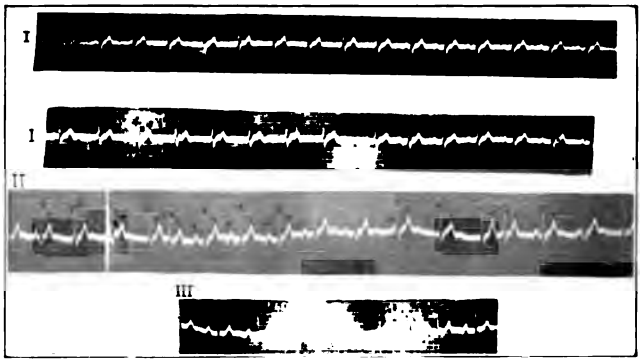

Fig. 6.—True extrasystoles.

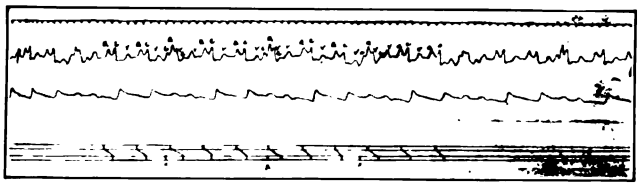

Fig. 7.—Jugular and radial pulse showing true extrasystoles. Diagram showing extrasystoles at *x*.

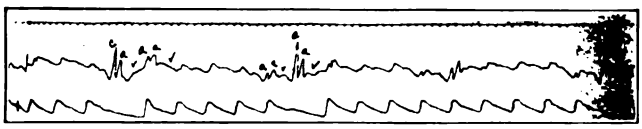

Fig. 8.—Polygraphic tracing of jugular and radial pulse; premature ventricular systoles with some arterial sclerosis and albuminuria, a type frequently found with nephritis.

traction of the ventricle with the usual development of the period of compensatory rest. Here we have a diagrammatic representation of the fact that the space preceding the abnormal beat plus the space following the premature contraction is equal to the distance between two normal heart cycles.

Auscultation of the heart sounds usually shows that no heart tones have been lost, for the abnormal beat is, in the majority of instances, accompanied by the first and second heart tones.

Auscultation of the heart tones also reveals the presence of the long pause after the premature beat.

Careful palpation of the radial pulse will usually reveal the presence of a small wave. At times, however, the small beat is entirely lost on the radial; indeed, the sphygmograph may even fail to show the faintest trace of a wave. It may or may not be evident in the carotid artery. As a matter of fact, some of these premature contractions of the ventricle may be so weak and so early that the semilunar valves at the aorta are not opened.

As a result we may have a change in the auscultatory phenomena. We may have the ordinary first and second sounds of the heart with the abnormal beat, or we may have only the first sound if the aortic valves are not opened by the premature contraction of the ventricle or, as happens in a few instances, even this first sound fails to materialize, or at least is not constantly audible. The latter condition must of course be very rare. The polygraphic and more particularly the electrocardiographic examination removes all doubt as to the real condition.

In some instances the premature contractions of the ventricle are grouped in such a manner as to give rise to the bigeminal pulse. In the bigeminal pulse (Fig. 2) every second beat is a premature ventricular systole. The premature beat in the radial is scarcely perceptible to the palpating finger and, indeed, it is at times not seen in the polygraphic tracing. The high peak in the

jugular—the c-a peak, unusually high and sharp, shows the combination of two elements, the ventricular and auricular phases coming practically at the same time. Such a pulse is often mistaken for heart block.

I desire to present a number of tracings which show premature ventricular systoles.

A study of the electrocardiograms with the radial pulse is of great clinical interest. Figure 3 shows two premature ventricular systoles. The deflection in both instances is downward and this (apex negative) deflection is followed by a very marked deflection upward, the time corresponding to the simultaneous "P" and "T" wave. There is a long compensatory pause, as may be seen both in the electrocardiogram and the accompanying arterial tracing (radial pulse). Following the premature ventricular systoles, there is a quickening of the heart action, due to a more rapidly following sinus stimulation. The two beats following the premature ventricular systoles follow more closely and then the normal rhythm is established, until the second premature ventricular discharge takes place toward the end of the tracing.

Figure 4 shows two tracings from the same patient. In Lead I the pulse is quite regular. In Lead II there are six premature ventricular systoles, the last four occurring regularly with the third beat of the heart.

The upper tracing (Lead I) shows a series of very regular beats with the "P," "R" waves well defined. The lower tracing shows four regular beats followed by a premature ventricular systole which precedes the "P" wave by a small unit of time. In this tracing there are six premature systoles of the ventricle. After the first premature beat there is a large downward deflection at a period corresponding to the time of auricular systole. There follows a compensatory pause with a normal heart cycle. Immediately following this normal beat there is the second premature ventricular systole with, however, a small upward deflection of the "R" wave. Following the "S" deflection, which is quite pro-

nounced, the "P" wave comes along just before the "T" wave, and there the "P" + "T" wave is exaggerated.

In this instance the patient has albuminuria, hypertrophy of the left ventricle and a somewhat enlarged aorta — Wassermann negative. Here, in looking for some extrinsic cause for the disturbance of the heart rhythm, I found a pronounced pyorrhea alveolaris. Pockets of pus were found from which large quantities of pus could be pressed. The patient was referred back to the family physician with the suggestion of immediate dental treatment.[1]

In certain instances, premature ventricular systoles may give the impression of the pulse of auricular fibrillation. It is evident that we should be on our guard because of the difference in prognosis and therapy. The tracings in Figure 5 might suggest fibrillation. The jugular curve, however, reveals premature ventricular systoles.

Figure 6 illustrates a form of premature ventricular systole which differs considerably from the usual type in that there is a fairly long series of premature ventricular systoles — the ventricular discharge rapidly encroaching on the preceding auricular stimulus until it precedes it by a definite interval. After eight such premature systoles the normal rhythm becomes established for a time. The upper two tracings in Figure 6 are from Lead I. In Leads II and III, we have not only premature ventricular systoles but in Lead II there are two true *extrasystoles* — the number of ventricular beats being in excess of the auricular beats. This case was one of rather mild endocarditis following a large abscess in the neck to the right of the thyroid cartilage.

Although it is usually assumed that true extrasystole occurs only when the pulse rate is rather slow, nevertheless, we have in the polygraph tracing shown in

1. I am informed by the family physician, June 14, 1916, that the treatment of the teeth has not only relieved the pyorrhea, but that the heart action is now absolutely regular.

Figure 7 an instance of a rather frequent rate with true *extrasystoles* thrown in between every third and fourth beat. The diagram illustrates that we have an increase of the number of ventricular beats above the number of auricular contractions. This case is one in which there is both tonsillar infection and pelvic disease.

I do not wish to multiply the number of illustrations of the subject. There are many more interesting phenomena in connection with premature ventricular systoles, but the tracings here presented are sufficient to bring out the main points.

SYMPTOMS

The occurrence of premature ventricular systoles may give rise to distinct subjective disturbances. These symptoms may be pronounced or they may occasion a mere passing discomfort. The degree of disturbance may be such as to occasion great alarm and this is particularly the case in neurotic or hypersensitive individuals. On the other hand, the grouping of the premature ventricular systole, as in the bigeminal pulse, may cause the patient comparatively little concern. There is, however, a temporary disturbance in the mechanism of the heart, and this alteration in the circulation is usually quite manifest in the violent pulsation in the neck. The patient may experience a disagreeable sense of suffocation, or, as happens in the premature beat of nodal origin, the auricle and ventricle contract at the same time, with the result that the jugular pulse becomes exaggerated. Again the beat following the compensatory pause may be, because of the greater filling of the ventricle, more pronounced and give rise to a distinct throb in the neck or in the head.

I find it impossible to dilate more fully on the possible symptomatology of premature ventricular systoles. Time does not permit of a full description of the individual symptoms.

ETIOLOGIC FACTORS

The frequency of premature ventricular systoles and their association with toxic conditions are matters of extreme importance in diagnosis and treatment.

This form of irregular heart action is found in connection with toxic conditions arising in the alimentary tract; in disease of the gallbladder; in infectious conditions arising in the accessory sinuses of the nose; in suppurative processes both acute and chronic; in diseases of the kidneys, and in conditions giving rise to high arterial tension. It is furthermore often attributed to the excessive use of tea, coffee and tobacco. Personally I have not been able to satisfy myself of the etiologic relationship of premature ventricular systoles and the use of tea, coffee and tobacco. These agents certainly have a decided influence on the circulation, and while I have frequently seen tachycardia resulting from the abuse of tea, coffeee and tobacco, and while the products so absorbed have a decided tendency to produce insomnia, I have not observed any such effects as premature ventricular systoles. While I recognize the possibility of tea, coffee and tobacco as possible agents in the production of premature ventricular systoles, we should not be too quick to assume this as a fact.

Formerly any decided irregularity of the heart action led to a diagnosis of myocarditis. However, one cannot have practiced medicine for any length of time without having been impressed with the fact that constipation is a factor of great importance and frequency in the etiology of premature ventricular systoles. It has been my expericence to notice the disappearance of such heart irregularity after the administration of a good dose of castor oil. I recall here the case of a patient of 70 years with hard arteries and pronounced premature ventricular systoles and where on account of the age and arterial disease, the diagnosis of a chronic myocarditis seemed at first justifiable. Here, to my great satisfaction the pulse became abso-

lutely regular after a thorough cleansing of the intestinal tract. Every trace of irregularity disappeared within twelve hours after the administration of castor oil.

Acute and chronic inflammation of the gallbladder have also, in my opinion, a place in the causation of premature ventricular systoles.

I have furthermore quite frequently seen the bigeminal pulse in cases of pronounced ptosis of the stomach and bowels. However, I am not inclined to attribute the development of premature ventricular systoles merely to the ptosis of the abdominal organs. Some authorities have spoken of a reflex from the displaced organs as the responsible factor in the production of too early contraction of the ventricle. This does not seem probable. It is much more important and much more satisfactory to attribute the irregularity to the toxic condition so commonly found in connection with dilatation of the stomach and ptosis of the bowels.

At times catarrhal and suppurative processes elsewhere, as for example about the female genital organs, and the accessory sinuses of the head, have a distinct tendency to alteration in the rhythm of the heart.

Only too frequently do we find persons with premature ventricular systoles refused life insurance. In one of my colleagues, the premature ventricular systoles have disappeared after successful treatment of a marked ethmoiditis. I have noticed a distinct tendency to the development of premature ventricular systoles in cases of stones in the gallbladder.

A very large proportion of other cases exhibiting premature ventricular systoles is found in cases in which there is a distinct evidence of disease of the kidneys. Such cases may or may not be accompanied by high blood pressure. It is clear that most of them have an excessive blood pressure. This has led to the opinion that the high blood pressure is the prime factor in the causation of the heart irregularity. When we

consider, however, that so many cases of chronic nephritis with high blood pressure have no such phenomena as the premature ventricular systole, we are forced to look for other causes than the high pressure alone. It is more than likely that the condition of the bowels and the toxemias of nephritis are the real factors. Free purgation and attention to the diet will have a beneficial influence on the heart.

Loss of sleep, worry and excitement, with their attendant wear and tear on the nervous system, have a distinct place in the etiology of premature ventricular systoles. Here again we have toxemias in the excessive use of the nervous system as the probable exciting factors, and we are therefore less and less inclined to speak of irregularities of reflex nerve action. As a matter of fact, as we develop in our knowledge of the physiology of the glands of internal secretion, the less we speak of reflex action on the heart. These cases are toxemias.

The more we study our cases of premature ventricular systoles, the more are we convinced that the vast majority of such cases, even though they have organic disease, are the subject of toxemias which temporarily disturb the rhythm of the heart. We are more and more inclined to the view that premature ventricular systoles are an expression of functional and not of organic disease. Time does not permit a discussion of all the factors or of all the varieties. Tachycardia of ventricular origin is a rare type and certainly a much more serious condition.

In view of what has been said in this short paper of the causative factors, little need be added to the subject of treatment. Look for the cause. At times it takes patience and all possible skill to find the source of the trouble, but that is our duty to the patient.

I am quite confident that this subject must appeal in a most practical way to those who are active in the great question of the risk to be accepted by life insurance companies.

I should certainly advise that cases showing premature ventricular systoles and no other sign of organic disease of the heart or kidneys be not considered bad risk. The life history of such cases should be an argument in favor of such a view.

Wenckebach in his work on heart irregularities speaks of patients with premature ventricular systoles improving under exercise, even such exertions as in mountain climbing. Such cases are no doubt a perfect demonstration that primarily the heart was not the seat of trouble. Evidently the exercise in the open air restored the secretions generally.

In a certain number of cases digitalis seems to have a good influence on premature ventricular systoles, and this may be explained by the effect of the drug on the vagus. Here there is a distinct tendency to slow the rate of contractions. We may assume that up to a certain point, digitalis controls the irritability of the heart. However, in a general way the immediate use of digitalis in premature ventricular systoles should not be looked on as good practice. In other words, one should first endeavor to find the cause, and by the removal of the cause wherever possible, remove the essential factors in the production of this type of heart irregularity.

PROGNOSIS

If there is no other evidence of disturbance of the heart, let the prognosis be favorable rather than unfavorable. Base your prognosis not on the presence of premature ventricular systoles, but rather on the underlying cause.

Union Central Building, Fourth and Vine Streets.

ABSTRACT OF DISCUSSION

DR. CHARLES F. HOOVER, Cleveland: The recognition of disturbances in the mechanism has after all not carried us much further in the handling and treatment of cardiac disease than twenty years ago. Twenty years ago we relied on a man having certain physical exercises. In recent years we attach a great deal of importance to the recognition of disturbances in the mechanism of the heart. That does not give

a clear conception of the heart's energy. We may have the same disturbances of mechanism in purely functional disorders of the heart as in organic lesions of the heart. As already pointed out many persons have functional disorders of the heart and at the same time evidences of infection and makes the suspicion that there is some direct relation between infection and functional disturbances. Again there is the psychic factor. Then the retrospective. I know of a patient who had premature ventricular systole after a period of several days and this was due to some disturbance in temperament. He was unable to swallow; when he swallowed his heart stopped. Instead of expectorating he would lie on his right side and allow the fluid to drool. The condition was very annoying. If he turned on his left side the heart would stop. The right side had a normal rhythm. His physical health remained about the same. The reason why these attacks ceased after five years was because he finally became convinced that he was not sick and did not have any organic disease of the heart. After all, in the recognition of disturbances in the mechanism of the heart we must rely on the fingers which can tell us the size of the heart, enables us to tell the conformation of the heart, the size of the auricle, the relative size of the ventricle, all this being tested out with exercises. Disturbances in the heart's mechanism can be incorporated with evidences showing that we are dealing with some organic lesion.

DR. WALTER J. WILSON, JR., Detroit: While the importance of premature systoles may be exaggerated, it is not a good plan to put them all into a class of functional disorders and be satisfied with that. If functional, it is pathologic physiology. The study of the arrhythmias has resulted in the great advance in the modern management of heart disease, and the presence of any irregularity demands most careful study as to diagnosis and prognosis. A more thorough knowledge of auricular fibrillation alone, has resulted in adding years to the lives of a great number of heart patients. The premature beats do often arise in acute infections. One patient with every attack of tonsillitis shows premature ventricular beats. The more severe types—and all sorts of combinations of premature beats may be observed, such as every alternate beat a premature beat—are more serious as to prognosis, one case later showing persistent pulse alteration. One patient under observation in 1914, in whom a series of premature ventricular beats of nine seconds duration was present, was most seriously ill, as such series came frequently and resulted in attacks of syncope. Premature beats are often associated with the more severe valvular lesions such as mitral and aortic stenosis. When present in the form of premature auricular beats in mitral stenosis, they are often followed by attacks of paroxysmal tachycardia, and not infrequently are the precursors of auricular fibrillation.

As to diagnosis the majority can be detected clinically by the stethoscope as the ventricle, not the radial pulse, should be our guide. As to treatment, digitalis is contraindicated except in the decompensated heart, as it renders them more likely to appear from the slow ventricular rate, while hyoscyamus or belladonna by quickening the ventricular rate submerges the premature systoles. In conclusion, while the majority of cases of premature beats are not of serious prognostic omen, a respectable minority require most careful attention.

THE SIGNIFICANCE OF PULSE FORM *

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The study of the pulse has occupied the attention of physicians from the very earliest times, and the pulse remains today one of the most accessible and important indications of the general condition of a patient. In studying the pulse the following data are noted: its rate, its rhythm, its tension, its size and its form. More precise knowledge concerning each of these is accumulating. The pulse rate, being an index of the heart rate, is of the greatest importance. In certain arrhythmias, the heart rate differs from the pulse rate because some ventricular contractions produce no palpable pulse beats at the wrist. This pulse deficit derives great significance from the fact that it indicates the amount of energy uselessly expended by the heart. Disturbances in the rhythm of the pulse have been carefully studied in recent years both by mechanical and by electrical methods. These studied have enabled us to classify the cardiac irregularities, to define their clinical significance, and to direct our therapy with greater precision than was formerly possible. Changes in the tension of the pulse are now recorded in terms of systolic and diastolic pressure, and the practical gain resulting from such records need not be emphasized.

Our knowledge of the size and form of the pulse has not kept pace with the advances in our knowledge of other pulse factors; and yet every physician, consciously or unconsciously, bases his opinion as to the

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quality of the pulse very largely on alterations in its size and form. For several years we have made records of the size and form of the pulse, and it is hoped that a presentation of some of our observations and impressions may be of service in the interpretation of observations that are made at the bedside.

The size of the pulse has been determined by measuring the volume of the waves recorded from a plethysmograph that encloses the hand, the forearm and the lower arm. The size thus determined usually varies from 0.4 to 1 c.c. An unusually large volume pulse usually occurs in aortic insufficiency (from 1.4 to 2 c.c.). In a given individual the size of the pulse is greatly affected by conditions of chilliness and warmth. When a person is chilly the pulse becomes smaller, whereas when he is warm it becomes larger. Variations in size from 0.26 to 0.96 c.c. have been observed under these conditions in a single individual. Of more clinical interest is the fact that during the febrile chill the radial pulse becomes smaller, and in some cases it almost disappears. As the chill abates and the patient begins to feel warm again, the pulse returns to its former size. It seems probable that the small pulse observed during a febrile chill is due to a local constriction of the peripheral arteries and that it does not necessarily indicate impending cardiac failure.

PULSE RECORDERS

About the middle of the past century, instrumental methods were introduced for studying the pulse form. Unfortunately two factors interfered with progress in such studies. In the first place the earlier instruments were subject to grave defects. In order to record the rapid changes of pulse form an instrument must itself be capable of performing rapid movements. Frank and Petter have estimated that an instrument should have a vibration time of not less than 32 per second in order to follow accurately the movements of the pulse in the peripheral arteries and that much

more rapid rates are required of instruments which are used to record the pulse in arteries lying near the heart. Since the sphygmographs and manometers in common use vibrate at rates of from 5 to 16 per second, the records obtained by such means are necessarily defective and hence there arose the discussions as to what part of the records were due to "flings" or other instrumental defects. To Otto Frank belongs the credit for having analyzed the theoretical requirements of pulse recorders and for having developed an instrument which will follow accurately the contour of the pulse curve. Frank replaced the usual recording lever on the tambour by a small mirror. This mirror reflects a beam of light, and the movements of this beam are recorded by photographic methods on a moving sensitized surface. Instruments of this type have been constructed which show vibration frequencies of 150 to 250 per second, rates amply sufficient to record the pulse in the central arteries.

The second difficulty in studying the arterial pulse of man lies in the fact that instruments cannot, as in animal experiments, be attached directly to the artery. Variations in arterial pressure can act on the recording device only through the medium of the vessel wall, the intervening tissues and usually some elastic receiver applied to the skin. Our inability to control these factors introduces an element of uncertainty in all pressure records taken from man. For this reason we have preferred to record the volume pulse in the arm by placing the latter in a plethysmograph which is connected with a Frank recorder. The apparatus used shows a vibration frequency of from 50 to 110 per second, a rate which is sufficient to record the peripheral arterial pulse. In the interpretation of our tracings we have been aided by momentarily obstructing the veins leading from the plethysmograph by a pressure cuff. When this is done, changes in arm volume are due almost entirely to movements of blood in the arteries leading into the plethysmograph.

TYPES OF ARM PULSE

Records of the volume pulse obtained by this method allow one to distinguish two main types of peripheral pulse in man. In the first, or sustained pulse, the sudden entrance of blood during early systole is followed by a gradual decline that is broken to a greater or lesser extent by the dicrotic and smaller secondary waves (Fig. 1). The second type of pulse is characterized by an abrupt diminution in arm volume immediately after the entrance of the primary pulse wave (Fig. 2). On palpation this gives the impression of a poorly sustained or bounding pulse. In the records the primary wave is pointed and the pulse appears collapsing. It may therefore be described as a poorly sustained, pointed or collapsing pulse. In this pulse the smaller secondary waves are usually absent. The dicrotic wave, however, varies greatly, from marked dicrotism to an almost complete absence of this wave. We believe that the poorly sustained or pointed character of such a pulse is of more fundamental importance than is the size of the dicrotic wave. If the veins leading from the plethysmograph are momentarily obstructed so that no blood can escape from the arm by this channel, it is readily demonstrated that the sudden drop which occurs in such a volume pulse just after the entrance of the main wave is due to a backward movement of blood in the arteries, caused as we believe by a reflection of the primary pulse wave out of the arm.

This pointed type of pulse can be produced in young individuals by therapeutic doses of nitroglycerin or of amyl nitrite. Of particular interest, however, is the fact that it occurs with great frequency during infectious diseases. We have noted it particularly in tuberculosis associated with fever, in typhoid fever and in most severe infections. When circulatory failure threatens during the course of an infectious disease, the pulse is practically always of a pointed character (poorly sustained). At the same time the size of the

pulse becomes progressively smaller and its rate increases. We believe that an understanding of these pulse changes would throw much light on the nature of the circulatory failure in the infectious diseases.

Relation to Blood Pressure.—The relation of pulse form to blood pressure is neither definite nor constant. As a rule, patients with arterial hypertension show a sustained pulse; but if nitroglycerin be given, the pulse may assume a pointed form even though both systolic and diastolic pressures still remain far above normal. Patients with abnormally low pressures are prone to show a pointed pulse, particularly if suffering from febrile disease. The association with low pressure is not constant, however, for we have records of sustained pulses where the systolic pressure varied from 90 to 100 and where the diastolic pressure varied from 65 to 70.

Relation to Vascular Tone.—The form of the peripheral pulse is certainly influenced by the condition of the peripheral arteries. The pointed pulse produced by nitroglycerin, for example, is to be attributed to a relaxation of the arteries. Conversely, fairly large doses of pituitary extract, when injected into a patient with a pointed pulse, will often cause the latter to assume a sustained character. Pituitary extract acts mainly by constricting the arteries. It seems certain, therefore, that the form of the pulse is dependent in large part on the tone of the blood vessels.[1]

Just how vascular relaxation leads to a pointed type of pulse is not altogether clear. In the arm of man, at least, nitroglycerin causes no unusual escape of blood from the arteries into the capillaries, nor is the flow of blood in the arm unusually rapid in febrile conditions. The change in pulse form produced by pituitary extract is likewise not accompanied by any

1. Both nitroglycerin and pituitary extract may also influence the cardiac output, but so far as we know the output is if anything increased by nitroglycerin and diminished by pituitary extract. Such changes would, as we shall see, tend to produce pulse forms of an opposite type to those actually observed during the action of these drugs.

constant change in the rate of blood flow through the arm. Finally a very rapid rate of blood flow through the arm, such as can readily be produced by exposure to heat, is not accompanied by a pointed pulse. It is evident, therefore, that the sudden decrease in volume is not due to an escape of blood into the arm capillaries. As has been said, the escape of blood which causes the abrupt fall of volume just after the entrance of the primary pulse wave is due to a backflow in the arm arteries themselves, owing to a reflection of the primary pulse wave. Such a reflection is favored by local vascular conditions in the arm. These consist (*a*) in a relaxation of the larger arm arteries that permits a large pulse wave to enter, and (*b*) in a constriction of the arterioles in the arm which increases the reflection of the waves that reach them.

Relation to Cardiac Output.—There are reasons for believing, however, that the pointed pulse cannot be explained solely on the assumption of changes in the local vessels of the arm. In fever the pulse wave which enters the arm is often unusually small. Furthermore, the pulse obtained by pressure over the carotid and subclavian arteries in such patients often shows a pointed form, and Wiggers[2] has published pressure tracings taken from the central arteries of animals which show a sudden fall of pressure during late systole. It is possible that a relaxation of the arteries or arterioles in other parts of the body may play a rôle in such cases, but of this we have little direct evidence.

On the other hand, there is reason to believe that a small or brief systolic output from the heart may contribute to the production of the pointed type of pulse. In auricular fibrillation it sometimes happens that the larger waves are of a sustained character, whereas the smaller waves are collapsing (Fig. 3). These smaller waves are superimposed on a relatively high diastolic

2. Wiggers, C. J.: Studies on the Pathological Physiology of the Heart, Figure 4, III, Arch. Int. Med., July, 1915, p. 140.

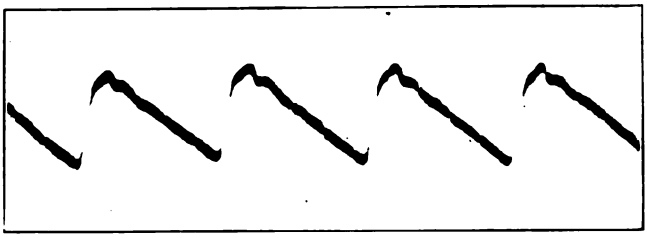

Fig. 1.—Sustained pulse of extreme type. Hypertension. Rate, 54.

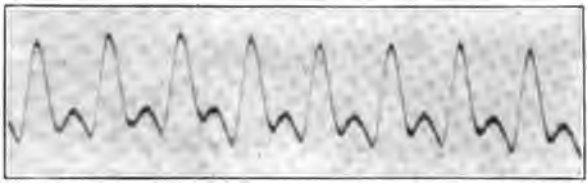

Fig. 2.—Poorly sustained or pointed pulse during fever. Rate, 110.

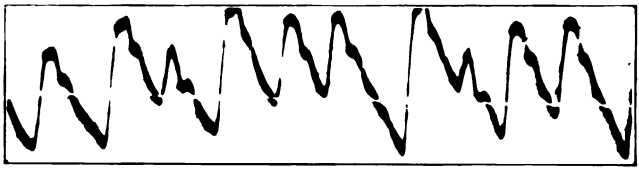

Fig. 3.—Auricular fibrillation. Note that the larger pulse waves are of the sustained type, whereas the small waves are pointed.

pressure, but otherwise the vascular tone may be regarded as constant. In such conditions the pointed pulse must be caused by a small or brief output from the heart. In various forms of tachycardia also the pointed pulse may be attributed to a small or brief systolic output. Finally, the pointed pulse has been observed toward the end and just after the Valsalva experiment.[3] This is independent of blood pressure variations, and is probably to be attributed to a small systolic output at these times.

THEORY OF THE POINTED PULSE

In seeking an explanation for the foregoing facts, I wish to call attention to two more or less divergent assumptions as to the nature of the pulse. According to the first and more simple explanation, the larger arteries act like an elastic bag which takes up the blood expelled from the heart and converts the intermittent into a continuous flow. Any fall of arterial pressure during a pulse cycle is attributed to an escape of blood into the capillaries. With a given resistance this escape is somewhat more rapid at high than at low pressures, but no adequate explanation can be given for the very sudden fall of pressure sometimes observed in the central arteries during late systole or for the backflow of blood in the brachial arteries of man during the sudden fall of volume that characterizes the pointed pulse.

According to the second explanation for the arterial pulse, the latter is essentially a wave which spreads over all parts of the arterial tree and is subject to the well known laws which govern wave motion. Ordinarily this wave is of such a character and meets such resistances that it fills the arterial tree promptly and almost uniformly so that the latter behaves for all practical purposes like an elastic bag. This gives rise

3. Lewis, T.: The Influence of the Venae Comites on the Pulse Tracing, with Special Reference to Valsalva's Experiment, and Dicrotism: a Note on Anacrotism, Jour. Physiol., 1906, xxxiv, 391. Similar changes in pulse form have also been recorded by the method described in this paper.

to the sustained pulse. Under other circumstances, however, the laws governing wave motion become more apparent and must be taken into consideration in attempting to explain changes in pulse form. I would suggest that the sudden fall of pressure which is at times observed in the central arteries toward the close of systole is due to the fact that as a wave passes along an elastic tube it causes an abrupt rise followed by an abrupt fall in pressure, even though there has been no actual backward displacement of the fluid. Similarly the retrograde movement of blood in the arm of man which characterizes the pointed type of pulse can be explained only as a reflection of the pulse wave. The pointed type of pulse, therefore, is one in which for some reason wave motion in the arterial system is particularly evident. Such wave motion would tend to be accentuated by a variety of circumstances, among which are a sudden expulsion of blood from the heart or a relaxation of the larger or smaller arteries. Even though the resistance encountered in the arterioles were sufficient to maintain a good blood pressure, the pointed pulse might still occur, owing to changes in these other factors.

PULSE FORM IN FEVER

In fever the pulse is usually rapid and of a pointed form. In size it may be normal or small. As circulatory failure threatens, the rate becomes more rapid, the pointed or poorly sustained character becomes more pronounced, and the size lessens. Doubtless the increasing rate is in part responsible for the other changes; yet the physician would hesitate to base his opinion solely on the recorded pulse rate or on the rate plus the blood pressures. He resorts to palpation of the pulse, and in doing so gains further information as to its size and quality.

What causes the small size and the poorly sustained quality of the pulse in serious infections? Are they due to arterial relaxation alone? In studying this

question we have observed that when pituitary extract is administered to patients showing a pulse of this type, the pointed form can often be converted into a sustained form. Invariably, however, this change is accompanied by a further decrease in pulse size. It seems probable, therefore, that while the pointed character of the febrile pulse is due in part to a relaxation of the larger arteries, this is not the entire explanation for the febrile pulse. The small size seems to indicate that there is in addition a small systolic output from the heart.

The explanation just given is in accord with the view that is now most widely held concerning the nature of circulatory collapse in surgical shock and in the acute infections. According to this view, the difficulty lies in an insufficient blood supply to the heart, owing either to stasis in the abdominal veins or possibly to an oligemia. Henderson has shown that in the type of shock which he studied there is a diminished output from the heart, owing to a lessened supply of venous blood. At first, however, there is no fall of blood pressure, owing to a compensatory constriction of the finer arterioles. Not until the blood stream was reduced to about one third did a rather sudden fall of pressure occur. As yet we have no accurate data concerning the rate of circulation in man during the circulatory collapse of surgical shock and the acute infections. I suspect that such studies will show a reduced circulation. If this should prove to be the case, the attention given by physicians to the size and form of the pulse in surgical and infectious conditions will receive a rational explanation. By palpation the physician gains an impression as to the size of the cardiac output in these conditions.

THE RELATION OF CHANGES IN THE FORM OF THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM TO FUNCTIONAL CHANGES IN THE HEART*

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Constancy of form is one of the most striking characteristics of electrocardiograms obtained at various times from the same individual. Any change in form is therefore of interest, as it indicates some alteration in the passage of the impulse of contraction through the heart or some change in the manner of the muscular contraction. Changes in heart rate and in the force of contraction are not, as a rule, accompanied by definite alterations in the form of the electrocardiogram.

The ventricular portion of the electrocardiogram is composed of a series of waves and is initiated by a group of three waves, the so-called Q, R, S group. Of these, only the R wave is constant in normal individuals in records obtained by the three leads of Einthoven. There are at present differences of opinion as to the functional activity of the ventricles responsible for this group of waves. Without taking up the various points in this controversy, it may be said that the evidence is in favor of the hypothesis that it is the passage of the impulse through the ventricles rather than the actual muscular contraction which gives rise to this part of the electrocardiogram and initiates the ventricular complex. As Einthoven[1] has suggested this Q, R, S group deserves a closer examination than has been hitherto given to it in clinical electrocardiography, as it shows the path by which the excitation wave is conducted from the auricles to all parts of the ventricular walls. It is to changes in this initial part of the ventricular electrocardiogram that attention is directed in this paper.

* Submitted for publication July 16, 1916.

* From the Department of Internal Medicine, Washington University, St. Louis.

1. Einthoven: Different Forms of the Human Electrocardiogram and Their Significance, Lancet, London, 1912, i, 853.

Before discussing the type of change to be described, it is necessary to consider several well-defined abnormalities of the ventricular complex which are frequently encountered in clinical electrocardiograms, and which are well understood, because they have been repeatedly reproduced under experimental conditions. The commonest of these is that caused by the passage of impulses arising in some abnormal point in the ventricles, the so-called ectopic stimuli, which give rise to ventricular premature contractions or extra systoles. When this occurs the impulse passes through the ventricles in abnormal directions, yielding a ventricular complex which is, as a rule, much deformed.

Another well-defined abnormality of the ventricular complex is caused when an impulse which reaches the ventricles by the usual path is hindered in its passage throughout the ventricles by a derangement of one of the branches of the conducting system which should convey the impulse either to the right or to the left ventricle. Such a condition of bundle-branch block has been produced in animals by cutting one or the other of the main branches of the conducting system. This procedure is followed by a great change in the form of the electrocardiogram, as first described by Eppinger and Rothberger.[2] Electrocardiograms similar to those obtained after this experimental procedure have been obtained from patients whose hearts have later shown, on histologic examination, a lesion of one or the other of the main branches of the conducting system. A sufficient number of cases have been studied to justify the diagnosis of the lesion from the type of the electrocardiogram. Carter,[3] who reported twenty-two cases of bundle-branch block, has pointed out the requirements of the form necessary to establish the diagnosis. The initial Q, R, S group of the ventricular complex exceeds the normal time 0.1 second; the waves are large, of bizarre forms, and the final deflection T is directed oppositely to the initial ventricular wave.

Changes in the distribution of muscle mass between the two ventricles, as occurs in cardiac hypertrophy, also leads to alterations in the form of the electrocardiograms, which is especially noticeable when the records obtained by the three usual leads are compared with one another. These changes have been recently demonstrated experi-

2. Eppinger and Rothberger: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med., 1910, lxx, 1.

3. Carter: Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle, THE ARCHIVES INT. MED., 1914, xiii, 803.

mentally by Fraser.[4] They are especially noteworthy in cases of congenital malformation of the heart. That the marked changes in the form of the electrocardiogram which occur in this condition are dependent on the abnormal distribution of the muscle mass between the two ventricles has been clearly demonstrated recently in our laboratory by McCulloch.[5] One other change in the form of the electrocardiogram remains to be mentioned, which is frequently encountered clinically, namely, alterations in the size or direction of the final wave of the complex, the so-called T wave. This wave, which is normally a long, well-defined upwardly directed wave, may become diminished in size, disappear or become inverted. Such a change is frequently observed in heart disease, especially when the myocardium is damaged. Kraus and Nicolai[6] have laid stress on the inverted or negative T wave as an indication of myocardial weakness, and probably all who have made use of the electrocardiogram in the study of clinical material will agree that this change frequently accompanies other signs of myocardial disease. The fact, however, that such a change takes place in the T wave when digitalis is administered, as pointed out by Cohn, Fraser and Jamieson,[7] renders its significance uncertain as an indication of myocardial weakness. It is mentioned here as being the one change in form of the ventricular complex which has been hitherto recognized as giving evidence as to the functional efficiency of the heart muscle.

The object of the present paper is to discuss a series of records which show changes in the form of the ventricular electrocardiogram differing from those that have been mentioned. These changes consist in alterations in the form of the Q, R, S group which are apparently dependent on a functional derangement of the ventricles, hindering the normal spread of the impulse of contraction. The spread of the impulse is hindered in some cases because the conducting system of the ventricles has not had a sufficient time to recover from the effects of an impulse that has just caused a ventricular contraction, while in other cases the recovery of the intraventricular conduction is abnormally

4. Fraser: Changes in the Electrocardiograms Accompanying Experimental Changes in the Rabbit's Heart, Jour. Exper. Med., 1915, xxii, 292.

5. McCulloch: Am. Jour. Dis. Child., 1916, xii, 30.

6. Kraus and Nicoli: Das Elektrocardiogram, Leipzig, 1910, p. 278.

7. Cohn, Fraser and Jamieson: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, Jour. Exper. Med., 1915, xxi, 593.

delayed, so that the impulse spreads through the ventricles properly only after a prolonged period of ventricular rest. In some instances in which a prolonged rest does not occur the electrocardiogram is of a form which indicates that the proper spread of the impulse through the ventricles is constantly lacking. Changes in form of the complexes have been observed to occur from time to time parallel to the clinical course of cardiac cases. A consideration of these changes indicates that the electrocardiographic method may demonstrate functional deficiency of the conducting system in the ventricles and in this way be a means of revealing diminished functional capacity of the ventricles.

The records have been obtained by means of the Edelmann type of string galvanometer. In all instances the tension of the string has been so adjusted that the passage of two millivolts through it, with the patient in the circuit, results in a deflection on the record of two centimeters. Only those records have been used in which this adjustment did not render the string sufficiently slack to cause any marked fling, which results in a definite deformity of the curves. Omitting this precaution leads to striking errors. In lettering the curves the single letter R is used to mark the Q, R, S group.

CASE 1.—J. B., a man, 42 years of age, had been aware of an irregularity of the pulse since boyhood. Except for a heightened blood pressure (systolic 148 mm. of mercury, diastolic 95), moderate cardiac enlargement and a trace of albumin in the urine, he gave no signs of disease. He had never had a serious acute illness, and his only excess had been very constant hard work as a lawyer. His life had always been one of unrestricted activity. An examination was undertaken only as a means of determining the type of cardiac arrhythmia. Electrocardiograms (Fig. 1) revealed a sino-auricular block, a complete cardiac cycle being omitted every few beats. The arrhythmia was complicated, however, by the occurrence of an idioventricular beat, always occurring near the end of the long pause caused by the missed beat and immediately before the auricular contraction which initiated the restoration of the regular rhythm. This idioventricular beat yielded a complex practically identical with that of the normal beats, indicating that it arose in the junctional tissues before the division of the conducting system, and that the impulse spread through the ventricles in a normal manner.

The special interest in this record centers on the complexes yielded by the ventricular responses to the auricular contractions which occur immediately after the onset of the idioventricular contractions. The records furnish twenty-five examples of this combination. The electrocardiograms show that the ventricular responses to these auricular

contractions vary with the time that elapses between the onset of the idioventricular beats and the auricular contractions. When this time is less than 0.15 of a second, usually no ventricular response follows the auricular contraction. As this time lengthens the ventricles respond, but when it is only a little longer than 0.15 of a second, the response is abnormal, as indicated by a prolonged auriculoventricular conduction time and by a markedly deformed ventricular complex.

The longer the time between the onset of the idioventricular contraction and the following auricular contraction, the shorter becomes the auriculoventricular conduction time and the nearer to the normal becomes the form of the ventricular complex. The more abnormal ventricular complexes show a prolongation of the time occupied by the Q, R, S group, which distinctly exceeds the normal time of 0.1 of a second. Both the ascent and descent of the R wave is more gradual than normally and there is a blunt, notched, or broken apex to the R wave, which is often distinctly diminished in height. The complexes are those to which Lewis[8] has applied the term "aberrant."

These changes in the ventricular complexes of the electrocardiogram are interpreted as follows: At times the impulse from the auricular contraction reaches the ventricles when they are still in the refractory phase, and so no ventricular response results. Usually the impulse reaches the ventricles when they have only partly recovered, and the conduction through the ventricles is depressed under these conditions, the impulse is delayed in part of the usual course, or follows an abnormal course, being blocked along some of its usual paths. Thus the intraventricular conduction apparently shows the same depression as is present in the auriculoventricular conducting system. The prolonged auriculoventricular conduction time is in part responsible for the degree of recovery which takes place in the ventricles, as this adds to the time between the idioventricular contraction and the ventricular contraction which follows.

The electrocardiograms of this case illustrate the changes in the form of the ventricular complex which are caused by functional derangement of the ventricles, when a contraction occurs before the ventricles have fully recovered from a previous contraction. They indicate also that the degree of abnormality of the complex parallels the degree of depression of the intraventricular conduction.

8. Lewis: Observations on Disorders of the Heart's Action, Heart, 1912, iii, 279.

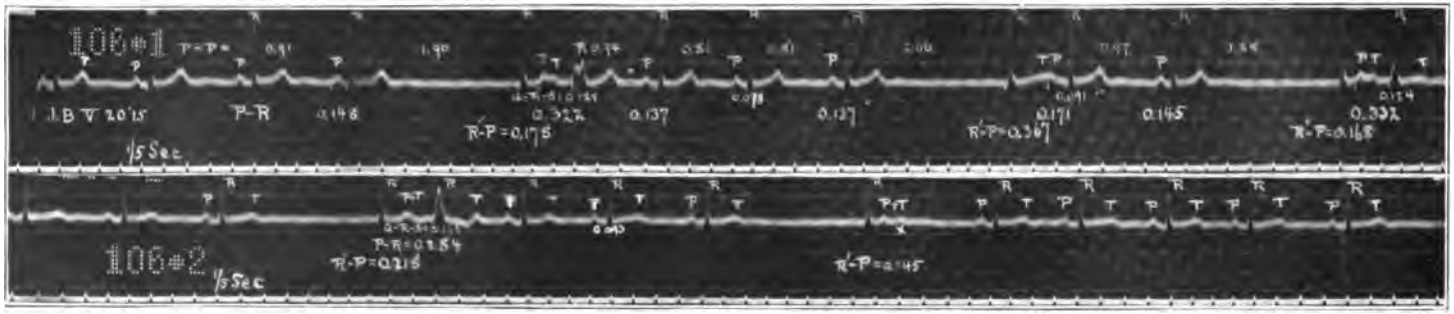

Fig. 1 (Case 1).—Sino-auricular block, with idioventricular contractions before the ventricles have recovered from a previous contraction. The abnormal ventricular complexes are yielded by contractions which occur

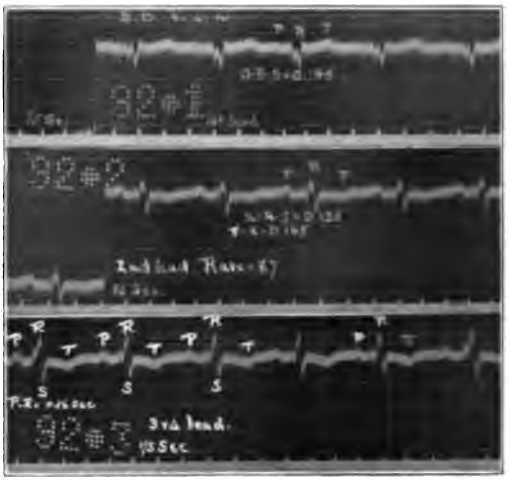

Fig. 2 (Case 2).—First record, May 2, 1915. Form of ventricular complexes abnormal in all leads. The Q, R, S time is prolonged; P-R time normal. The patient showed signs of marked cardiac decompensation.

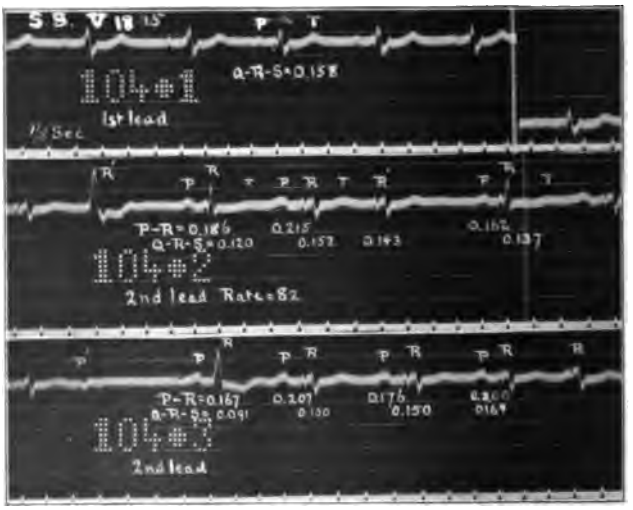

Fig. 3 (Case 2).—Second record, May 18, 1915. The form of ventricular complexes differs from that seen in Figure 2. The Q, R, S time and the P-R time are distinctly prolonged. The form of the ventricular complexes are more nearly normal after a prolonged ventricular rest. The patient showed distinct clinical improvement.

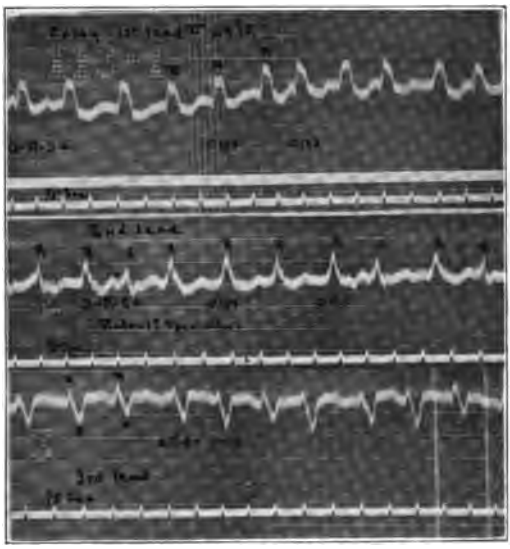

Fig. 4 (Case 3).—May 24, 1915. Auricular fibrillation; very rapid ventricular rate, with markedly deformed ventricular complexes.

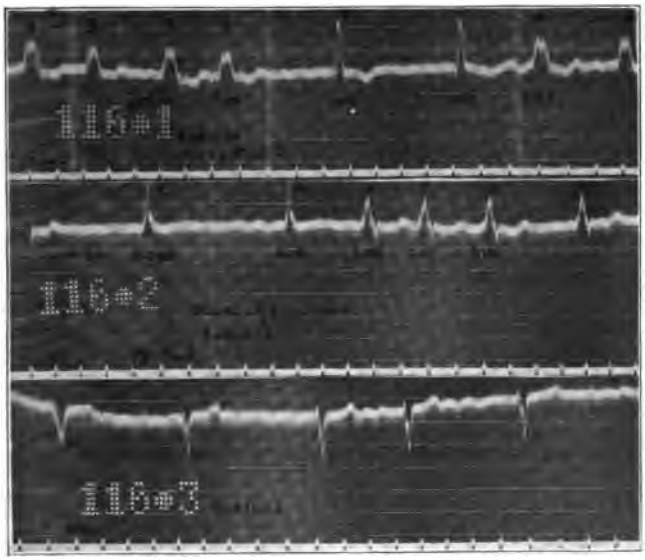

Fig. 5 (Case 3).—May 26, 1915. Auricular fibrillation; after taking tincture of digitalis for forty-eight hours. Striking change in the form of the ventricular complex after ventricular pauses, especially in the first lead.

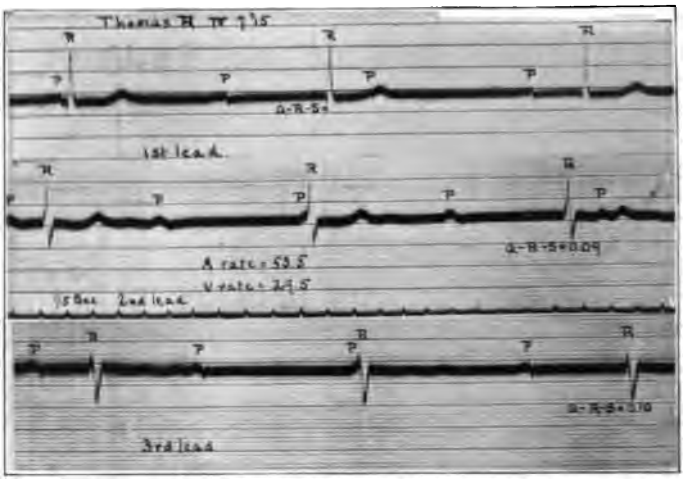

Fig. 6 (Case 4) —April 7, 1915. Complete heart block; the usual type of ventricular complex; normal Q, R, S time.

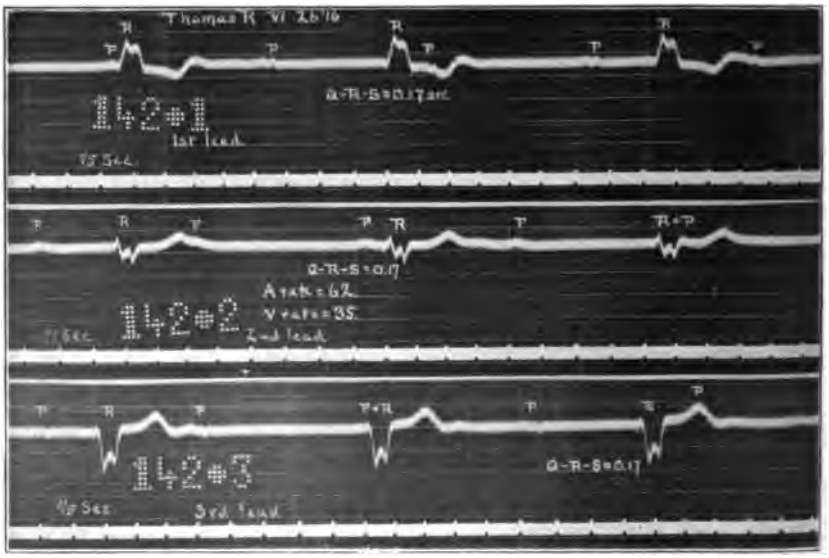

Fig. 7 (Case 4).—June 26, 1915. Striking change in form of the ventricular complex accompanying severe symptoms. Compare with Figure 6.

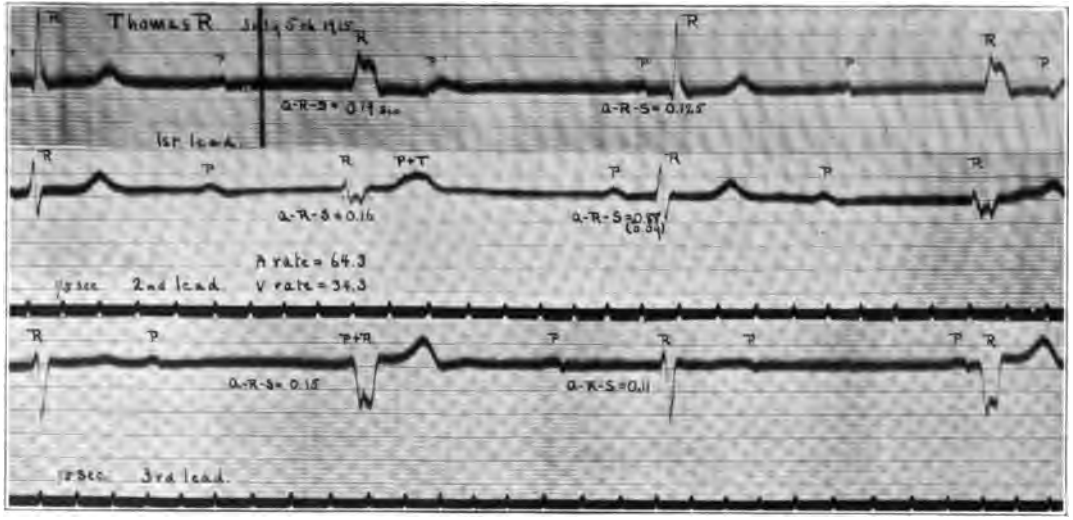

Fig. 8 (Case 4).—July 5, 1915. The form of the complexes alternate; first the usual form and then the form that appeared nine days previously.

Fig. 9 (Case 4).—July 5, 1915. Transition between the old and the new forms of the first lead complexes.

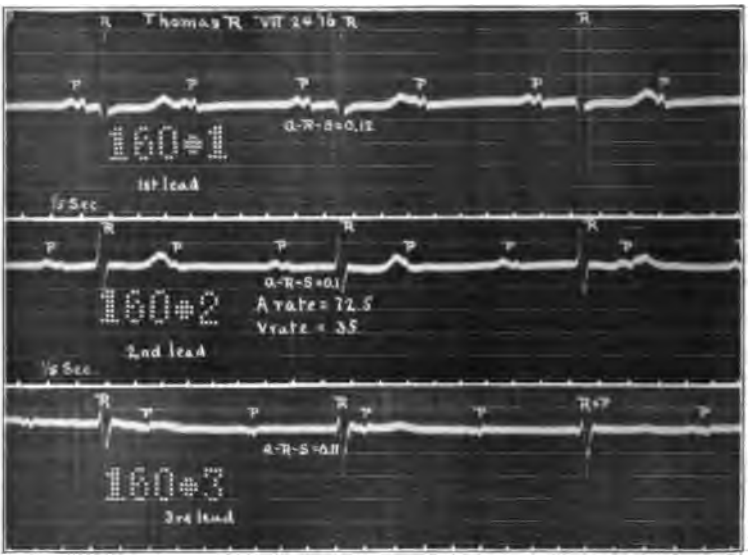

Fig. 10 (Case 4).—July 24, 1915. The form of the ventricular complexes is constantly that seen before the marked change occurred. No further change occurred.

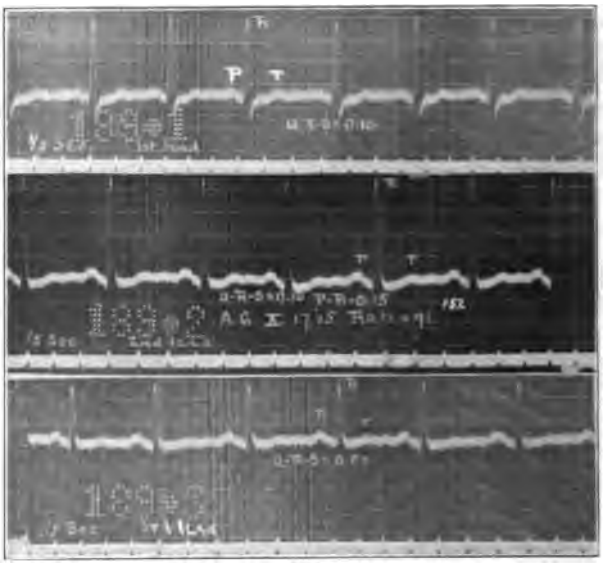

Fig. 11 (Case 5).—Oct. 17, 1915. Cardiac efficiency but slightly impaired.

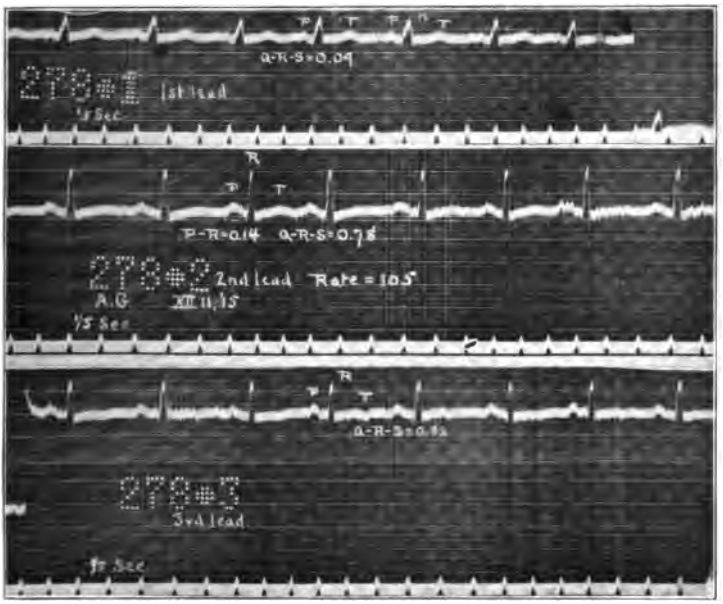

Fig. 12 (Case 5).—Dec. 11, 1915. Cardiac efficiency much impaired.

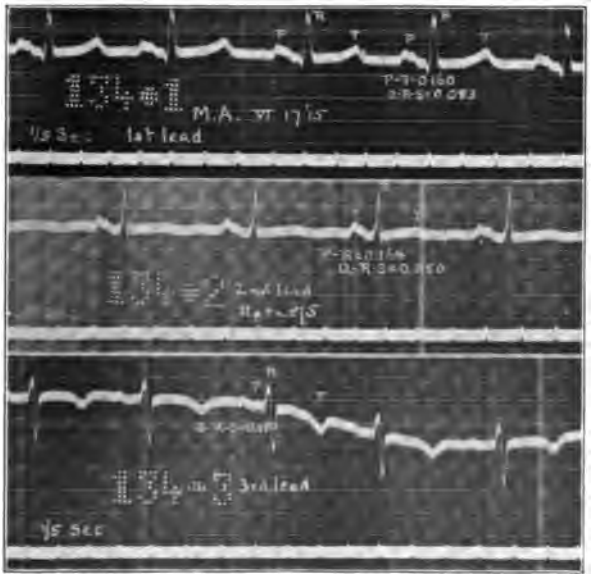

Fig. 13 (Case 6).—June 17, 1915. Marked signs of cardiac decompensation.

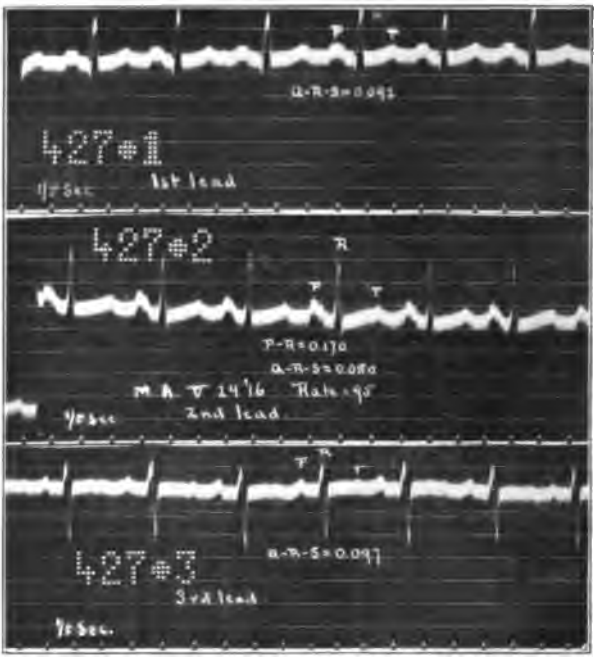

Fig. 14 (Case 6).—May 24, 1916. Patient much improved; cardiac decompensation slight.

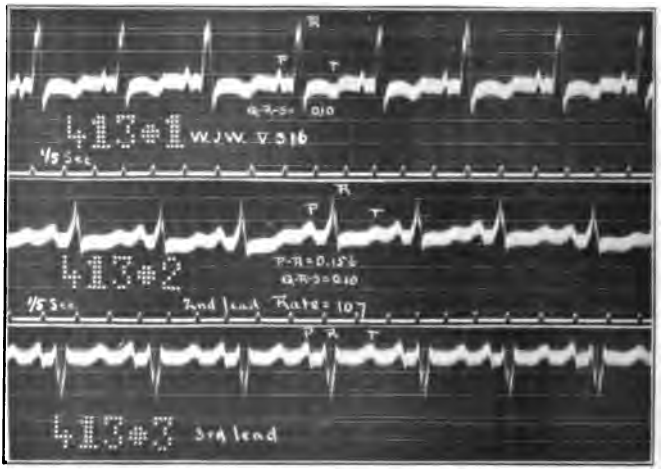

Fig. 15 (Case 7).—May 3, 1916. Patient showed signs of extreme cardiac decompensation.

CASE 2.—S. B., a woman of 63 years, suffered from atrophic cirrhosis of the liver, chronic myocarditis and chronic valvular cardiac disease (mitral insufficiency). On May 2, 1915, when the first record was made, she was cyanotic, markedly dyspneic, and there was general anasarca. The heart was much enlarged, cardiac dulness extending 18.5 cm. to the left of the midsternal line, and besides the systolic murmur in the apex region there was a pericardial friction rub. The heart was beating at a rate of 87 per minute, and the systolic blood pressure was 110 mm. of mercury, the diastolic 65 mm.

The electrocardiograms (Fig. 2) are very abnormal in form. The Q, R, S group is composed of a series of waves, none of which resemble those of the normal electrocardiogram. The period of time occupied by the occurrence of this group of waves is distinctly longer than the normal 0.1 of a second.

On May 18, when electrocardiograms were again obtained (Fig. 3), the patient was much improved. The dyspnea, cyanosis and edema were distinctly less. The systolic blood pressure had risen from 110 to 120 mm. of mercury without change in the diastolic pressure. The heart rate was 82 per minute. The electrocardiograms show an arrhythmia caused by premature contractions of auricular, nodal and ventricular origin. There is a distinct change in the form of all ventricular complexes as compared with those seen in Figure 2. The most striking feature of the record is the change in the form of the ventricular complexes which occur after a period of increased ventricular rest. This change is seen after the compensatory pause following premature ventricular beats and when premature auricular beats are blocked. Under these conditions the ventricular complexes are much more nearly normal in form.

This case illustrates that changes in the form of the ventricular complexes may occur with improvement of the cardiac efficiency, as evidenced by the clinical improvement, and with increased periods of ventricular rest. The usual diastolic pause between the regular beats was not long enough to allow the intraventricular conduction to recover sufficiently to allow the impulse to pass normally. This case is, therefore, an example of those in which the recovery of the intraventricular conduction is abnormally delayed, so that the impulse spreads through the ventricles properly only after a prolonged period of ventricular rest.

CASE 3.—A man, 33 years of age, came into the outpatient department complaining of pain in the chest and shortness of breath. The heart dulness extended 5 cm. to the right and 15 cm. to the left of the midsternal line. The heart sounds were distant and blurred, and the heart was beating very rapidly and irregularly. The electrocardiograms (Fig. 4) obtained on this day show a heart rate of 174 per minute. The ventricular complexes occur irregularly and are of unusual forms, while no auricular complexes are visible. The main ascents and descents of the Q, R, S group are gradual, and the time occupied by this group is distinctly prolonged, but difficult to determine accurately. The slight variation of form from beat to beat may be caused by combinations of ventricular complexes with the waves of auricular fibrillation. The patient refused to remain in the hospital. He was put on digitalis and returned in

forty-eight hours, after two drams of the tincture had been taken. On this admission there was distinct improvement in symptoms and the heart rate was greatly reduced, varying from 77 to 100 beats per minute. Electrocardiograms (Fig. 5) obtained this day are typical of auricular fibrillation. The arrhythmia is much more marked, and after the longer diastolic pauses, the ventricular complexes have a much more normal form than after the shorter pauses. This is especially noticeable in the first lead, where the abnormal, blunt, low complexes, composed of an R wave with a slow ascent and descent become, after prolonged diastoles, sharp pointed, higher waves resembling closely those usually seen in auricular fibrillation. A study of the various records convinces that this change in form is not caused by combinations of the ventricular complexes with the waves of auricular activity. The fact that this patient died suddenly two days after his second visit, when under a severe emotional strain, suggests that the heart muscle was badly damaged.

The case is one in which the ventricles responded to impulses from the fibrillating auricles at a very rapid rate, and the periods between contractions were not of sufficient duration to allow complete recovery of the intraventricular conduction. The cardiac slowing which resulted from the administration of digitalis caused some improvement in this respect, and resulted in longer ventricular rests, which were followed by ventricular contractions yielding normal or nearly normal complexes.

CASE 4.—A man, aged 59, suffering from syphilis and complete heart block, was under almost continuous observation for a period of nearly two years, during which time numerous electrocardiograms were obtained. During the first six months he had many attacks of unconsciousness and convulsions, with prolonged periods of ventricular inactivity, giving the typical picture of Stokes-Adams syndrome. After March, 1914, these did not occur, and electrocardiograms similar to those shown in Figure 6 were constantly obtained until June 26, 1915. On this day a marked change in the form of the ventricular complexes was noted (Fig. 7). It is seen that a marked change occurs in the form of the Q, R, S group in all leads and the time occupied by the group greatly exceeds the normal. The broad form with the notched top seen in the first lead is especially noteworthy, as it resembles closely the abnormal form seen in the first lead of the first and third cases.

On the day before the record was made the patient had three short "sinking spells," in which he became semiconscious. These spells lasted two or three minutes only and came on just as the patient was about to "drop off" to sleep. These spells continued for several days and gradually disappeared. There was no change in the pulse rate at these times of syncope, it remaining between 35 and 43 per minute. During the time when these attacks of syncope occurred the patient was in a critical condition. There was marked cyanosis, dyspnea, Cheynes-Stokes respiration and collections of fluid in the chest, peritoneum and lower extremities. His death was expected hourly, and there seemed to be extreme cardiac insufficiency. But he gradually improved, and July 5 he was much better, the cyanosis, dyspnea and edema being less marked. On this date electrocardiograms (Fig. 8) showed another change in

form. The following note was made just after the records were taken: "Electrocardiograms taken this afternoon show a very interesting alternation in the form of the Q, R, S group of the ventricular complexes. They are first of the type formerly seen and then of the type which appeared constantly a week or so ago. There is apparently no difference in the effectiveness of the ventricular contractions yielding the varying complexes, as no alternation of the pulse is noted in an examination made directly after the records were obtained, either by palpation of the radial pulse or by auscultation over the brachial artery with the sphygmomanometer applied. The systolic blood pressure is 105 mm. of mercury, the diastolic 45. All beats come through with equal intensity."

At first sight one would be inclined to interpret these changes in form as being caused by contractions set up by impulses arising from two distinct foci, resulting in the passage of the impulses along two different sets of paths. A record obtained with the first lead, however, is evidence for the belief that the impulse of contraction was spreading properly through the ventricles only in alternate beats (Fig. 9). It is seen in this record that a transition form occurs (the third and fifth complexes), suggesting that the spread of the impulse was either not always complete or was not at the same rate through each ventricle. This conception of the variations in the spread of the impulse seems to explain these transition forms of ventricular complexes more satisfactorily than assuming the presence of a shifting focus of stimulus formation.

By July 27, 1915, the patient's condition was greatly improved. He no longer had dizzy spells and was able to be up and about. The electrocardiograms on this date were of the same form as seen previous to the period of marked cardiac insufficiency (Fig. 10).

This case shows a transient but extremely marked change in the form of the ventricular complexes during complete heart block, occurring during a period of great cardiac insufficiency. The abnormally slow rate of the ventricles allows the element of functional fatigue alone to be ruled out. Here the intraventricular conduction was so deranged that the long ventricular pauses at first did not lead to its recovery, while later the intraventricular conduction was apparently normal or partially recovered in alternating beats. Finally the form of the complexes returned to what must be considered the normal for this case, showing that the functional derangement of the ventricles responsible for the change in form was transient.

CASE 5.—A colored woman, aged 30, suffered from a generalized infection with *Streptococcus viridans,* acute endocarditis, embolism, cardiac dilatation and hypertrophy and syphilis. On Oct. 17, 1915, she had moderate dyspnea. The cardiac dulness extended 3.5 cm. to the right and 12 cm. to the left of the midsternal line. The heart rate was 91 per minute, while the systolic blood pressure was 120 mm. of mercury, the diastolic 72. There were no marked signs of cardiac insufficiency. The electrocardiograms obtained on this day showed high R waves, with sharp ascents and descents in all leads (Fig. 11).

On Dec. 11, 1915, the patient was very ill and showed definite signs of decompensation. The systolic blood pressure had fallen 27 mm. of mercury, while the diastolic pressure was unchanged. The heart rate was 110. The outline of cardiac dulness was unchanged. Electrocardiograms (Fig. 12) show a distinct change in form of the ventricular complexes, the R waves being much less high, and the ascent and descent, especially in the first lead, being slow. The Q, R, S time is not, however, definitely changed.

In this case well-defined changes in the ventricular complexes occurred synchronously with distinct decrease in cardiac efficiency. The form of the complexes resembles sufficiently those accompanying definite functional depression in the previous cases to suggest that the change which occurred during failure of the cardiac efficiency is the result of the cardiac failure and indicates presumably derangement of the intraventricular conduction.

CASE 6 is an example of change in form of the ventricular complex which occurred synchronously with a marked improvement in symptoms and apparently because of functional improvement of the ventricles. The patient was a woman of 24 who suffered from aortic and mitral insufficiency and who showed at times alternation of the heart beat. On June 17, 1915, when the record shown in Figure 13 was obtained, there was dyspnea while at rest in bed and other signs of cardiac decompensation. The electrocardiogram shows a slightly slowed ascent and descent in the R waves, and in Lead I the blunt, split-topped form is seen, which suggests that seen in some of the previous cases.

These abnormalities are less marked, and almost absent in records obtained on May 24, 1916 (Fig. 14), when the patient was no longer in the hospital, but returned merely for observation. On this day there was slight dyspnea after walking to the heart station, but no other symptoms suggesting cardiac insufficiency.

The change in form in the ventricular complexes which accompanied marked improvement of the cardiac efficiency seems to indicate that the abnormalities of the complexes observed during definite decompensation were dependent on the cardiac insufficiency. The fact that in this case alternation of the heart beat was not accompanied by alternation in the form of the ventricular complexes is evidence in favor of the belief that the abnormalities seen in Figure 13 were not caused by changes in muscular contractions as such, and makes it appear more likely that they resulted from defective conduction of the impulses through the ventricular musculature.

CASE 7 is included as one of marked cardiac decompensation, which showed abnormal ventricular complexes similar to those seen in the previous case. The electrocardiogram (Fig. 15) was obtained from a man with aortic insufficiency of syphilitic origin, whose heart was evidently much dilated. Here again the gradual ascent and descent of the limbs of the R waves are seen,

especially in the second lead. The same blunt, notched wave is seen in the first lead, while the third lead complex is distinctly peculiar. The patient died suddenly a few days after the record was obtained, following the intravenous administration of strophanthin. It seemed not unlikely that ventricular fibrillation resulted from the administration of the drug.

COMMENT

The idea that changes in form of the ventricular complexes may depend on faulty conduction through the ventricles of impulses descending from the auricles was first suggested by Lewis.[9] He based his hypothesis on records obtained under experimental conditions, as well as on electrocardiograms from clinical material, and developed his idea further in a second paper.[8] He points out the association of prolonged auriculoventricular conduction with the so-called aberrant contractions, and suggests that abnormal complexes may depend on damage affecting special branches of the intraventricular conducting system. Under such conditions the impulse is at one time transmitted through the whole arborization, while at other times it passes into the arborization, but fails to course along certain given channels.

Hart[10] has also recognized derangement of intraventricular conduction as a cause of contractions yielding abnormal ventricular complexes. He shows records in which the Q, R, S group of the complex is deformed in a manner somewhat similar to deformities described in this paper and he believes that the abnormalities are caused by damage to the musculature, so that the passage of impulses is interfered with in all parts of the conducting system.

The occurrence of varying ventricular complexes in cases of complete heart block has been reported by Cohn[11] and by Oppenheimer and Williams.[12] These cases have been interpreted as examples of either a shifting focus of stimulus formation within the ventricles or as interference with intraventricular conduction. The changes in form of the ventricular complexes of the case reported here are considered as dependent on interference of ventricular conduction.

9. Lewis: Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature, Heart, 1910, ii, 23.

10. Hart: Paroxysmal Tachycardia, Heart, 1912, iv, 128.

11. Cohn: A Case of Transient Complete Auriculoventricular Dissociation, Showing Constantly Varying Ventricular Complexes, Heart, 1913, v, 5.

12. Oppenheimer and Williams: Prolonged Complete Heart Block, without Lesion of the Bundle of His and with Frequent Changes in the Idioventricular Electrical Complexes, Proc. Soc. Exper. Biol. and Med., 1913, x, 86.

The purpose of this paper is not primarily to record a series of cases showing derangement of intraventricular conduction. This change in function is discussed only as affording an explanation of the changes in form of the ventricular complexes which have been observed. The object of the paper is to point out certain abnormalities occurring in electrocardiographic curves which apparently accompany functional deficiency of the ventricles. This is done with the hope that the electrocardiographic method may sometimes prove of value in determining changes in the functional capacity of the ventricular musculature, perhaps the most important and one of the most obscure problems involved in the study of the heart.

Only a much wider experience and a collection of many such cases as those exemplified in this paper can determine the value of these observations from the purely clinical point of view.

SUMMARY

A series of cases is reported which yielded electrocardiograms showing abnormal ventricular complexes. These abnormalities consist in changes in the initial portion of the complexes, the Q, R, S group, and differ from those yielded by contractions caused by ectopic stimuli and from those changes which occur with bundle-branch block.

These abnormalities are apparently dependent on derangement of the intraventricular conduction, which prevents the passage of the excitation wave either along the usual paths or at the usual rate throughout the ventricles.

The normal spread of the impulse is hindered because the impulse reaches the ventricles before the conducting system has recovered from the preceding contraction, and the records indicate in some cases that this derangement disappears with prolonged ventricular rest.

These observations are taken as evidence for the belief that in cases in which the ventricular complexes constantly show certain abnormal forms, there are functional changes in the heart which prevent the normal recovery of intraventricular conduction during diastole. It is shown that changes in form of the ventricular portions of the electrocardiogram may occur synchronously with functional changes in the heart, and evidence is offered for the belief that certain abnormalities in the form of the electrocardiogram indicate functional derangement of the ventricles.

SOME FACTORS IN THE PRODUCTION OF CARDIAC DYSPNEA*

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The symptoms most commonly complained of by patients with heart disease are palpitation, precordial pain and shortness of breath. The latter, often only noticeable on exertion, is perhaps the most frequent cause of subjective distress, so that for this reason, as well as on account of its seriousness, dyspnea is a symptom worthy of considerable attention from the clinician. A full realization of the significance of dyspnea, and a properly adapted therapy, can only be the outcome of a much more complete understanding of the pathologic physiology underlying it than we possess at present. In all probability it will be found to be a complex phenomenon which can be analyzed into several types, and in the cause of which numerous factors combine in varying degrees. Some of the etiologic factors concerned with the production of dyspnea in heart disease are already recognized fairly definitely, and it is to a consideration of these that the present paper is directed.

It will be well, at the outset, to state exactly what is meant by the term "dyspnea" for, curiously enough, although the word is in everyday use, there is apparently no generally accepted accurate conception of its significance. It is often considered to be synonymous with either rapid respiration or unusually deep respiration, but neither of these in themselves constitute dyspnea. As the derivation of the word implies, there

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

is a subjective element, an element of discomfort or of difficulty in breathing. This discomfort may depend on either an increase of the rate or of the depth of respiration, but usually it is associated with an increase in both, and depends fundamentally on a hyperpnea, or increase of the total amount of air breathed in a given unit of time. Technically, it is customary to express the pulmonary ventilation, or the amount of air breathed, in liters per minute, and this is referred to as the minute-volume. Dyspnea is present when the minute-volume approaches the maximum of which the subject is capable.

Thus, for instance, a healthy adult at rest may breathe approximately 500 c.c. per respiration, and at a rate of twelve respirations per minute. The minute-volume will then be 6 liters. On walking slowly about the room the metabolism is increased and the minute-volume of air breathed will rise nearly threefold, to about 15 liters. On walking up a flight of stairs the minute-volume may become 20 liters. Neither on walking about the room nor going upstairs, however, does the normal subject become dyspneic. By increasing somewhat both the rate and depth of his respiration he is able to raise the minute-volume from 6 to 20 liters without any appreciable subjective sensation. When, on the other hand, he begins to run, and his metabolism becomes increased so that it requires a ventilation of 60 to 70 liters a minute, he becomes dyspneic, for he has usually approached both the maximum rate and depth of respiration of which he is capable. An athlete in good training can ordinarily breathe much deeper than the individual of sedentary habits, and he may be able to raise the volume of air breathed to 80, 90, or even 100 liters a minute without any definite feeling of distress.

In brief, then, the production of dyspnea resolves itself into the problem of the relation between the demand for an increased pulmonary ventilation and

the ability of the subject to meet that demand by increasing the rate and depth of his respiration. This somewhat artificial statement of the situation purposely omits reference to one very important factor, namely, the rate of the circulation. The fundamental purpose of the respiration is, of course, to promote gaseous exchange in the body tissues and this is only effected through the medium of the blood. A slow blood flow would interfere with the process of metabolism as much as would an insufficient pulmonary ventilation. One of the results, however, of an inadequate blood flow would be a further stimulation of the respiratory center. The data available with regard to the rate of the circulation and especially concerning its relation to pulmonary ventilation are so scanty and unreliable that it seems best at present to keep the attention focused wholly on the external respiration.

The factors which may produce dyspnea are, in the first place, those which cause an increase of the minute-volume of air breathed, and, in the second place, those which abnormally limit the ability of the subject to meet this increased demand. As causes of an increase in the minute-volume of air breathed there are, apart from nervous and psychic influences, three main factors to be considered: a rise of metabolism, an acidosis, and any change in the physical condition of the lungs which results in a less efficient utilization of the air breathed. The causes which tend to prevent the increase of ventilation are chiefly those which interfere with the depth of the respiration and cause a decrease in the "vital capacity" of the lungs.

In what degree, then, are these various factors to be considered as playing a part in the production of dyspnea in cardiac disease?

What, in the first place, is the state of the body metabolism? The information now at hand is based chiefly on work done in the bed calorimeter at the Russell Sage Institute for Pathology in New York, which has been subsequently confirmed and amplified

by observations with the Tissot spirometer at the Peter Bent Brigham Hospital in Boston. The results show that in well-compensated patients the metabolism is within the normal limits, while in patients who are on the edge of decompensation, or who show some slight dyspnea even at rest, the metabolism is often, but not at all regularly, some 20 to 40 per cent. above the normal. Unfortunately, it has not been possible, for obvious reasons, to study severely decompensated patients. It is quite probable that in such cases the metabolism would be found to be considerably higher, but even were it double the normal, the rise in metabolism could only be regarded as in itself a minor factor in the production of dyspnea.

Much attention has been recently devoted to the rôle of acidosis as a cause of dyspnea in heart disease, but as yet its true significance is not wholly clear. It is possible that in certain acutely decompensated patients with pure cardiac disease, during the period when they are having severe dyspnea even while at rest in bed, there may be some slight acidosis which stimulates the respiratory center, causing an increased pulmonary ventilation. The condition is, however, transient and disappears quickly as compensation is regained. Acidosis is certainly a more imporant element in those cases in which cardiac insufficiency is associated with severe renal lesions. In them an acidosis frequently develops secondary to the nephritis. In a small percentage of instances with uremia the acidosis may be of such high degree as to cause hyperpnea resembling that of diabetic coma, but even in the more common mild grades of acidosis it has been shown to be a factor which renders the patient unusually sensitive to the production of dyspnea. While acidosis may thus play a part in the causation of dyspnea in many advanced cases of cardiorenal disease, it has not been shown to be of importance in cases which are even moderately well compensated or are without severely injured kidneys.

The significance of physical changes in the lungs in the production of hyperpnea has been demonstrated by studies with the spirometer, which show that the minute-volume of air breathed by patients with heart disease may be considerably increased, even quite apart from an abnormally high metabolism or an acidosis. Patients who are wholly without dyspnea while they are quiet may be found to be breathing 9 or 10 liters of air a minute instead of the usual normal of about 5. Since the total metabolism is approximately normal, the output of carbon dioxid per minute is normal, but as the volume of air breathed per minute is increased the expired air contains a percentage of carbon dioxid which is less than normal. These patients may be perfectly comfortable while at rest, but their reserve is greatly interfered with, and they suffer as soon as they begin to move. The minute-volume of a normal person walking slowly about in the room is about three times as great as it is while he is sitting quietly. Thus, if he breathes 5 liters a minute at rest, he will breathe nearly 15 liters when performing this exercise. A cardiac patient will show a similar relative increase of ventilation, but as he may be breathing 8 liters a minute at rest, the volume on walking will rise to nearly 24 liters. The cardiac patient is thus distinctly nearer to the maximum of which he is capable, especially when, as will be shown, his maximum is much less than that of the normal person. This increase of the pulmonary ventilation seems to bear a close relation to changes in the vital capacity of the lungs, and it may depend on the fact that there is a decrease in the respiratory surface of the lungs without a corresponding change in the dead space, so that a larger amount of air must be breathed in order to obtain the normal amount of oxygen per minute. While an increase in the minute-volume of air breathed due to such a cause is found not only in patients who are acutely decompensated, but often in those who are quite comfortable while at rest, it is,

nevertheless, of importance only in the rather severe cases.

Such are the factors concerned with the production of dyspnea which act by increasing the pulmonary ventilation. As opposed to these there is at least one important feature which makes it difficult for the cardiac patient to meet a demand for an increase of his pulmonary ventilation. This is his inability to breathe deeply. An accurate index of the degree to which the depth of respiration is limited may be had by measurement of the vital capacity of the lungs, which is the volume of the greatest expiration after the deepest possible inspiration. This is regularly below normal in cardiac patients who complain of dyspnea. It has long been known that many persons with heart disease cannot breathe as deeply as normal individuals, but the significance of this fact has been rather disregarded. It is, however, readily appreciated when one considers that a rise of pulmonary ventilation is brought about by increasing the rate and depth of breathing, but best and most economically by increasing the depth. If, then, a patient with heart disease is unable to increase the depth of his respiration as well as a normal person, he will be at a distinct disadvantage when he begins to exercise and his metabolism rises. On account of his inability to breathe deeply, the maximum amount of air that he can breathe per minute will be below the normal, and a grade of hyperpnea that will cause no symptoms in a healthy individual, will produce in him the subjective sensation of dyspnea. There is, indeed, a very close relation between the decrease in the vital capacity and the tendency of a patient with heart disease to become dyspneic. In a large series of cases in all stages of cardiac disease the decrease in the vital capacity has been found to run almost constantly parallel to the degree of physical disability. Practically all patients who give a history of abnormal shortness of breath on exertion are found to have a vital capacity below normal, and the more prominent the symptom,

the lower the vital capacity. This decrease in the vital capacity characterizes both mild and severe cases of heart disease in so far as they have a tendency to dyspnea, either while at rest or on moderate exertion, and it seems to be the most constant factor in the etiology of the dyspnea.

Briefly, then, we may summarize by saying that in patients with heart disease a decrease in the vital capacity of the lungs is an important and practically constant feature in the production of dyspnea. Associated with this, and apparently depending on it, there is usually a hyperpnea in the more severe cases. In many severe cases further causes of dyspnea may be the presence of an acidosis, and, to a less extent, an increase of body metabolism.

ROENTGENOCARDIOGRAMS

POLYGRAPHIC SLIT TRACINGS OF CARDIAC PULSATIONS BY THE ROENTGEN RAY

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The purpose of this paper is to show the practicability of Roentgen-ray tracings of the heart beat and to arouse interest in this method of cardiac study.

It is sixty-nine years since Vierordt made the first tracing of the pulse. Marey, Dungeon, Jaquet and other clinicians of the first rank designed sphygmographs and interpreted tracings. But it was not until MacKenzie, barely fourteen years ago, working with a polygraph of his own manufacture, in a country practice in Scotland, recorded a body of observations single handed, that cardiac tracings became of recognized clinical value.

Einthoven in 1903 produced that miracle of delicacy and precision, the electrocardiograph. Gocht and Rosenthal in 1912 published a method of making polygraphic Roentgen-ray tracings of the movement of the heart. The term "roentgenkymography" was applied to this method. The paper of Gocht and Rosenthal is the only literature on the subject that I have been able to find.

It remained for the researches of MacKenzie, Lewis and many others to correlate cardiac tracings with the functions of the sinus node and the auriculoventricular bundle of His, and thus to translate polygrams and electrocardiograms into clinical terms. In consequence a new understanding of the irregular and disordered heart has been laid, on which has arisen a new nomenclature. Auricular fibrillations, heart

block, auricular flutter, alternation of the pulse, extrasystole, are terms which have thus passed into current medical literature. In conjunction with these, we are becoming familiar with such technicalities as the a c p or t wave or of the a c interval.

This flood of renewed interest in the old problems of the heart beat has left the whole subject of Roentgen tracings untouched. The brief paper of Gocht and Rosenthal dropped into the oblivion of scientific archives from which few papers ever return.

While recognizing the high merit of this preliminary announcement, it may be said that Gocht and Rosenthal demonstrated the possibility, rather than the practicability, of Roentgen tracings of the heart beat. At the present day we have the advantage of many improvements in Roentgen instrumentation and technic which combine to make roentgenocardiography a practicable clinical method. These improvements are, briefly, the Coolidge tube, ray filtration, the "Buckey effect" which is possible by the use of cellular slits, and safe and convenient tables.

The fact that Roentgen-ray installations have become very common makes it desirable to use them for the purposes of cardiac tracings in the place of an additional equipment like the electrocardiograph, which involves an expense equal to a Roentgen-ray machine. Any Roentgen operator is competent to make roentgenocardiograms, but special training is required to use and take care of an electrocardiograph. The polygraph and the sphygmograph are relatively inexpensive and will continue to be useful, although they are distinctly inferior to the electrocardiograph.

The Roentgen examination allows the clinician to determine the shape, size and position of the heart in the chest with a precision unapproachable by any other method. A visual study may be made of the character of the muscle movement of the different chambers from different angles. The cardiac sounds may be ausculted while the heart is beating visibly on the

Roentgen-ray screen. The aortic silhouette and pulmonary artery may be scrutinized, and finally without moving the patient from the table, polygraphic tracings may be made directly from the cardiac chambers.

A Roentgen tracing of the heart means to most medical readers a tracing of the outline of the heart. The subject of this paper, the roentgenocardiogram, is a tracing of the heart beat obtained by covering the heart with strips of sheet lead so arranged that a narrow slit in the lead can be adjusted over the pulsating margin of the cardiac silhouette as viewed by the Roentgen ray. Several of these slits can be adjusted simultaneously over different areas of the pulsating heart, the aorta and the pulmonary vein. A photographic film on a screen in a cassette is then made to travel at a given speed, transversely over these slits, while the Roentgen ray is turned on. The result is a tracing which is similar to and comparable with a sphygmogram, a polygram or an electrocardiogram.

For comparison: The electrocardiogram, as you all know, is a tracing obtained on a strip of photographic film which moves across a slit. Running at right angles to this slit is a very fine metallic filament which vibrates with the electric currents excited by the heart muscle. An electric light behind the filament prints the vibrations on the moving film. A microscope is arranged so as to magnify these vibrations and thus yield a tracing having the requisite amplitude.

In the case of the roentgenocardiogram the wire filament is replaced by the edge of the heart muscle itself and the light is replaced by the Roentgen ray. There is no other essential change. No microscope is required.

In the electrocardiogram we deal with the electrical changes in the heart; in the sphygmogram or polygram we deal with pressure variations within the blood vessels (excepting in the case of the apex beat); but

in the roentgenocardiogram we deal directly with movements of the heart muscle. The electrocardiogram is stated to give a record of both auricles contracting as a unit and of both ventricles contracting as a unit. The sphygmogram or polygram gives records of the venous pulse and the left ventricle. But the roentgenocardiogram is capable of giving a separate record of the muscle movements of each chamber of the heart. In this respect it stands unrivaled.

Tracings have been obtained experimentally by connecting the nose with a tambour and having the subject hold the glottis open during suspended respiration. Also tracings have been obtained from a rubber tube in the esophagus. The claim has been made that these tracings represent the pulsations of the right ventricle and the left auricle. But it may be stated that the roentgenologic method is the only one which can furnish unquestionable tracings of these separate chambers of the heart, and produce them so as to be clinically practicable.

It is evident that the polygraph, the electrocardiograph and the roentgenocardiograph, while recording different data, yet arrive at the same conclusions regarding cardiac irregularities. Auricular fibrillations, heart block or auricular flutter would be recognized in substantially the same way by any one of these instruments.

The electrocardiogram is a photomicrograph. The real amplitude of the oscillations of the wire filament between the field magnets is so exceedingly small that the microscope is required. The amplitude of the writing hand of the polygraph or sphygmograph depends on mechanical multiplication by levers and tambours. But the amplitude of the heart muscle movement is sufficient without the use of any means for magnification. Some increased amplitude is unavoidable, however, and it is easy to increase it still further.

In the case of both the polygram and the electrocardiogram there is a complexity of machinery between the heart of the patient and the tracing. But in the case of the roentgenocardiogram the heart writes its record directly on the film without essential intervention of anything whatever. In the case of the polygraph or sphygmograph the impulse which moves the levers and writing fingers is transmitted through a varying length of artery or vein and also through rubber tubing or levers. The jugular tracings are rendered impure by the impulse of the carotid. But the Roentgen tracings are necessarily free from any and all of these complications.

In the case of the electrocardiograph we are working with one of the most complex and delicate of modern clinical instruments. It is of foreign manufacture. Repairs and replacements are likely to be difficult, expensive and subject to long delays. In the case of the roentgenocardiograph we are working with a Roentgen-ray equipment which is largely standardized and made in this country. The addition required for the average Roentgen laboratory is so essentially simple that it can be made extemporaneously by the average mechanic, excepting for the motor or clockwork which runs the cassette carriage and marks the time.

The polygraph has the disadvantage that, in a large proportion of cases, it is impossible to secure a venous tracing from either neck or liver. The electrocardiograph when in order and free of vibrations has very few disadvantages. However, it is, of course, necessary that the patient remain free from muscle movements during the taking of a tracing. The contraction of any muscle excites an electric current. To bend a finger is to mark a tracing. Patients with exophthalmic goiter, paralysis agitans or any other disease associated with involuntary muscle movements are not suitable for the electrocardiograph. The position of the heart in the chest is also of the

greatest importance. A preponderance of heart muscle to the right would reverse an electrocardiogram. Three leads are used and three tracings made as a rule with each patient.

The disadvantages of the roentgenocardiograph are:

1. Very large, heavy patients offer resistance to the passage of Roentgen rays. This is overcome by using wider slits, a slower movement of the carriage and a ray of higher penetration.

2. Some patients with cardiac disease cannot lie in the horizontal position. This difficulty can be overcome by the sitting position, in which case the patient is placed with the back against the lead screen of the cardiograph and with the tube in front. Each slit must then be adjusted over an interspace between ribs, and especial pains must be taken to immobilize the patient.

3. Patients with advanced tuberculosis, pneumonia or pleuritic or pericardial effusions are not suitable for Roentgen tracings, because the outline of the heart is obscured or actually concealed. Dense deposits at the hilum of the lung running downward along the heart border usually are an advantage rather than otherwise, because there is a narrow clear space between the heart and these deposits which improves the tracing.

Some electrocardiographs are equipped with tambours so that ordinary polygraphic tracings may be run simultaneously with the electrocardiogram. Valve sound tracings may also be included. The roentgenocardiograph may likewise be equipped with tambours and a sound recorder. The Roentgen ray is an ideal agent for the registration of movements of metallic pointers.

The addition to a Roentgen-ray equipment which will enable the operator to make roentgenocardiograms is best illustrated by lantern slides. I use a simple, crude device made by my own hands. It remains for

some instrument maker to supply us with a properly made roentgenocardiograph. It should consist of a lead-covered table, having an open square of 8 inches in the middle. It is convenient to use 10 by 12 films in cassettes. The cardiographic table, therefore, should have a lead covered length of 12 inches beyond the opening in each end. This makes the table 32 inches long. The legs of this table should be adjustable so as to allow the table to be placed over the recumbent patient without touching the face or abdomen. A track and carriage allows the film to travel from one end of the table to the other over the opening. The carriage should be provided with a clockwork or motor which will give several speeds to the film. The average speed required is 5 cm. to the second. An accurate timing device is desirable, but accurate timers in use on the Roentgen-ray machine may be utilized so that a centimeter rule may be laid along a film to give time divisions if, for example, exactly 50 cm. of film have taken ten seconds of Roentgen-ray exposure.

Instead of a table and carriage, we may use a lead covered cylinder on which is rolled the intensifying screen and film properly protected from light. The rotation of the cylinder over a single long slit will provide the mechanical requirements, in a very compact form, for simultaneous tracings of the pulsations of the right auricle and left ventricle.

It is obvious that the narrower the slit or the faster the speed of the carriage, the sharper will be the line of the heart tracing, provided the Roentgen-ray exposure is properly measured. The average width of slit which is practicable is found to be 2 cm. The slower the transit of the film, the narrower may be the slit while preserving the same Roentgen-ray exposure of the film.

If the film travels 5 cm. to the second and the slit is 5 cm. wide, then the exposure of the film will be one

second. But 1/5 second is sufficient for a film on a screen in a cassette. Therefore our slit may be 1 cm. wide. But 2 cm. is an average which gives good definition and allows more latitude for differences in patients. In my experience a Coolidge tube, medium focus, set for a 5-inch spark gap and 33 milliamperes will stand the run for ten seconds without trouble. The distance of the anode from the film should average 24 inches.

In order to adjust the slit bars it is necessary to use the fluoroscopic screen. Two to three milliamperes with a tube set for 7 or 8-inch spark gap is ample.

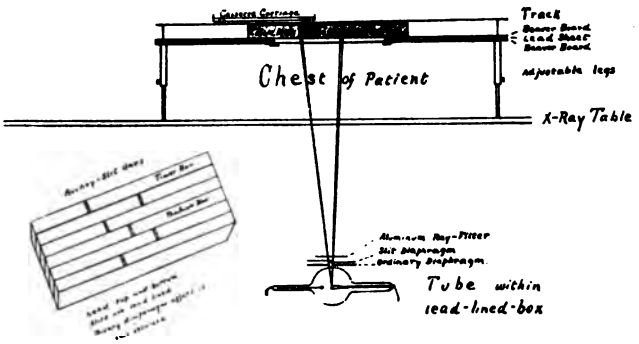

Fig. 1.—Device for making simultaneous tracings of the pulsations of the heart chambers and of the aorta, by the Roentgen rays.

Three mm. aluminum filter should be used to increase the time limit for observations. The erythema dose of Roentgen rays is stated to be from 25 to 30 milliampere minutes with an 8-inch skin distance, a 9-inch spark gap and 3 mm. of aluminum filter. At 16 inches this would give 100 milliampere minutes since the quantity of the rays decreases with the square of the distance. If we are using 33⅓ milliamperes we thus have three minutes of safe exposure. One-half minute of this time will allow three tracings of ten seconds each. We thus have 83+ milliampere minutes remaining at our disposal. A small fraction of this time will

have been used to examine the pulsating heart and to adjust the slit bars, leaving a wide margin of safety. The fact that the patient may be turned in other positions for additional tracings gives the opportunity for repeated observations within the limits of safety.

The use of a narrow slit of Roentgen ray provided by the slit diaphragm greatly extends the time limit of safety. Different sections of the heart silhouette may be used with each tracing, so as to give added information. This exposes new skin areas each time. The use of the film between two screens greatly lessens the exposure time. By these precautions the number of tracings permissible with safety would be beyond any number required for practical purposes.

The Roentgen-ray operator should estimate and know in each case exactly what quantity of Roentgen ray his patient is receiving, as a matter of system and record.

It will be noticed from these tracings that there is a striking dissimilarity between the movements of the right and left auricle. The right auricle frequently gives a nearly straight or faintly undulating line, while the left auricle at the same time gives a very definite curve. Again, the right auricle gives a curve of collapse while the left gives a curve suggestive of contraction.

The impression made on me by the Roentgen-ray study of the heart beat is that normally in man there is little or no muscle contraction of the auricles. The right auricle seems to fill steadily from the vena cava and to swell during ventricular systole. Then during ventricular diastole there is a subsidence which does not appear to be due to a muscular contraction. The extreme thinness of the auricular wall and the absence of valves at the mouths of the cava are understandable on this hypothesis.

The contraction of the right ventricle sends the blood through the lungs into the left auricle. We see a forceful distention of the left auricle followed by a

graded collapse. Just preceding this collapse there is an elevation of the ventricular muscle near or at the auricular-ventricular margin. This muscle elevation follows toward the center of the ventricle where it loses itself in the distention of the whole chamber. Repeated observations give the impression that the blood is sucked into the ventricle, and that the subsidence of the auricle is due chiefly to this fact and little or not at all to any muscular contraction of the auricle. Here again the extreme thinness of the auricular walls and the abscence of valves in the pulmonary arteries bear out this view.

Furthermore, there has been demonstrated a negative pressure of about 50 mm. of mercury in the left ventricle in man at the beginning of diastole. This negative pressure is not compatible with the hypothesis that the blood is forced into the left ventricle by auricular contraction.

There seems to be nothing about the study of the heart beat which is more unanimously agreed on than that the auricles normally have a muscular contraction of their own and drive blood into the ventricles. This view is not questioned by any authority that I have been able to consult. An exception is made of so-called auricular paralysis of perpetual arrhythmia. The whole subject of auricular fibrillation, heart block, flutter and extrasystole seems to depend on auricular contractions for rational explanations. The sinus node, the auriculoventricular node, the bundle of His, the origin of auricular or ventricular contractions in independent centers, seem to be woven into a firm fabric that stands the wear of repetition.

The difficulties are apparent, but the Roentgen tracings of cardiac movements impel me to search for other explanations. To my mind it is quite possible that further researches in comparative biology may show that the purpose of a special muscle bridge or bundle between the primitive tissue called the sinus

node and the ventricular muscle is to liberate the ventricles from auricular interference and allow atrophy of the auricular musculature. In lower forms with more primitive types of hearts, true auricular contractions do occur normally, but in man it seems to me this ability in the auricular muscle to initiate ventricular contractions is lost excepting in disease or abnormal states. These contraction waves in auricular centers independent of the sinus node may set up conduction waves in the ventricles with the production of irregularities.

The roentgenocardiogram shows particularly well the ventricular form of the right auricular curve when present, thus demonstrating small regurgitations through the tricuspid valve which are not discoverable otherwise. This ventricular form of the right auricular pulsation must be shown to be concomitant with a corresponding subsidence of the left auricular beat. A question arises concerning transmitted movements of a ventricular beat to other parts of the heart.

I have indulged in speculation and hypothesis in order to arouse the opposition which may lead to a trial of the Roentgen-ray investigation of the heart by clinicians who are not roentgenologists. It is in the belief that the roentgenocardiogram with the associated Roentgen-ray study of the working heart will prove fruitful in the understanding of cardiac physiology and pathology that I urge the practice of this method.

Fig. 2.—Apparatus in the upright position.

Fig. 3.—Apparatus in the horizontal position.

Fig. 4.—Roentgenocardiographic table viewed from above, showing slit bars and cassette carriage.

Fig. 5.—Roentgen image of heart, showing position of slits when adjusted over right auricle, left auricle and left ventricle.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. HEWLETT, ROBINSON, PEABODY AND CRANE

DR. FRANK N. WILSON, Ann Arbor, Mich.: Abnormal ventricular complexes in the human electrocardiogram may signify the presence of one or more of the following conditions: (1) Impulse formation within the ventricular conduction system below the bifurcation of the His bundle or within the muscle of the ventricular walls as in premature ventricular beats; (2) abnormal intraventricular conduction as in bundle-branch-block; (3) an abnormal distribution of the ventricular muscle as in right or left ventricular preponderance; or (4) a change in the electrical state or condition of the ventricular muscle as in the abnormal ventricular complexes showing inverted T waves obtained by the administration of digitalis to normal individuals. Dr. Robinson's paper deals with marked changes in the QRS group and this group of waves is affected, so far as I know, by the first three conditions only. The ventricular complexes of right and left ventricular preponderance are characteristic and entirely different from the abnormal complexes under discussion. Furthermore, the impulses in all but one of Dr. Robinson's cases were supraventricular in origin. We must assume, therefore, that abnormal intraventricular conduction was responsible for the abnormal complexes in these instances. I have seen abnormal ventricular complexes similar to those described by Dr. Robinson in several instances, but have not been able to correlate them with functional insufficiency of the heart. They have also been a permanent feature in the cases I have observed. One must believe that when this is the case there is an organic lesion of the ventricular conduction system rather than a functional depression of this system as seems to have been the case in the patients studied by Dr. Robinson. I have also seen instances in which only a single part of the QRS group was abnormal. For instance, I have several times seen in lead I a perfectly normal R wave associated with a very broad distinctly abnormal S wave. In such instances it would seem that a circumscribed lesion of the ventricular conduction system is present or that the functional depression of intraventricular conductivity is local rather than general. I agree with Dr. Robinson's interpretation of the curves he has shown and feel that his conclusions are justified at least so far as the cases he has studied are concerned.

DR. S. MARX WHITE, Minneapolis: I have been interested in trying to learn how far we can go in making a correct diagnosis of premature ventricular systole by polygraphic tracings independent of the electrocardiogram, since the latter is accessible to relatively few. The occurrence of extrasystoles can usually be detected by using the stetho-

scope, the first and second tones, or the first tone alone, being audible. What Lewis says about exercise is of value. In a study of about 150 cases we find that the use of exercise is of value in differentiating extrasystolic from other types of irregularity. Have the patient exercise. During the exercise the premature beats will lessen in number in the great majority of cases. Following rest there will be an increase in the number per minute and they will become very clearly defined. The point brought out about extrasystoles being functional should not be allowed to pass without more discussion. I am convinced that premature ventricular beats mean more than a functional disturbance. It may be that an increased tension in the heart wall is capable of exciting them, but a focus of increased irritability in the heart wall is also a likely source for premature beats. I am particularly interested in the cases in which infection is found about the teeth or tonsils. In these cases with focal infection I wish to call attention to the fact that such infection seems to have a predilection for the heart wall. I think we must look on these as cases in which there is an actual microbial infection of foci in the heart wall. It has been shown that in rabbits there is very frequently an infection of the myocardium when injected intravenously with fresh cultures of micro-organisms taken from the tonsils or the walls about the tonsils. Such small foci of myocardial infection may readily become foci for increased irritability and thus sources of extrasystole. I am skeptical and must be shown and have proven to me that this condition is functional. It must be shown definitely that there is no such change as I have suggested. We see acute infections and often an apparently complete recovery of the heart muscle. May we not have in the heart muscle small foci of inflammation producing extrasystoles and yet have recovery so that later normal function is restored?

Dr. Philip S. Roy, Washington: Has the reading of heart charts any relationship to the therapeutic treatment? Yes. I think every physician should have an apparatus for drawing the radial pulse, it is not necessary to have a time marker. With such an apparatus one will be aided greatly in his therapeutic treatment. Fibrillation of the auricle can be learned from a radial tracing. As regards therapeutic application, we all know that digitalis is a specific in fibrillation of the auricle although not curing the conditions causing it. There is another condition that causes much anxiety to both the family and the physican, Sinus arrhythmia, but so soon as the radial drawing is studied we learn that the condition is not a serious one. When we make charts we should learn how to recognize sinus arrhythmia, a condition which can be cured by belladonna. Another condition is extra systoles which in a large percentage of the cases, can be recognized by means of the radium charts. Then the

therapeutic application must be made. Another condition, a hopeless one, is pulsus alternans. I cannot make a diagnosis of this condition without a radial chart. Does the condition of the pulse always indicate the condition of the whole vascular system? I do not think so. In anaphylaxis shock the patient may be pulseless, yet the heart is doing good work. All should have an apparatus for radial tracings, if we wish to be fair to our patients.

DR. HUGO A. FREUND, Detroit: The polygraph and electrocardiograph have cleared up many things that we have not previously understood. The roentgenocardiogram will probably enlighten us further. There are a number of points, however, that should be established before conclusions are drawn. First, the stability of construction of the apparatus eliminating sources of mechanical error. Second, the projection of the ray. Third, the relative distance between the patient and the screen. All these will require standardization. If we could have an orthogonal projection and a tracing of such rays with the moving heart, then doubtless an accurate tracing would be assured. I wish to emphasize something of interest that I have noticed in reference to the changes seen in the Q, R and S waves. In those cases of slow ventricular rhythm where the deformity of the wave is as indicated by Dr. Robinson, the tendency to sudden cardiac failure exists. In cases of marked decompensation where a tendency of this complex to return to a more normal outline is seen under treatment, the prognosis for the time being is more favorable.

DR. FRANCIS W. PEABODY, Boston: The administration of an alkali will relieve the symptoms, as far as they are due to an acidosis in chronic nephritis, but it is only in exceptional cases that a definite clinical effect is obtained.

DR. ALBION WALTER HEWLETT, Ann Arbor, Mich.: In my opinion extra systoles arise from some part of the heart muscle which is unusually irritable and for this reason initiates a premature beat. The region initiating the extra systole may be very small and the heart muscle as a whole may be in good condition. Furthermore, the excessive irritability may be due, not only to organic disease, but to toxic influences or possibly to nervous changes. The presence of extra systoles is an indication for a careful heart examination but the prognosis depends on this examination rather than on the irregularity itself. Dr. Peabody's careful and extensive study of cardiac dyspnea has led to the conclusion that in the main this is due to changes in the lungs. It may be recalled in this connection that mitral lesions which cause pulmonary congestion are apt to be associated with early dyspnea, whereas aortic lesions cause dyspnea only in their later stages. Great possibilities for further studies of the cardiac mechanism are opened up by Dr. Crane's work. The

information thus obtained differs, however, from that furnished by the electrocardiograph for the reason that the records depend on mechanical and not on electrical changes associated with the heart's movements.

DR. JOHN ERNEST GREIWE, Cincinnati: Premature ventricular systoles are a functional disturbance. It should be our duty to look for and find the cause of such disturbance and by removing the cause, get rid of the trouble. To bring this subject home in a most practical way, let me recite briefly the experience of a man who had been operated for appendicitis. On the second night after the operation, the patient had an irregular pulse. This alarmed both nurse and physician, who immediately resorted to subcutaneous salt solution, with the result of producing a large slough over the breast. The irregularity, as I later discovered, had often been present and as the patient afterward remarked, "I could have told them immediately not to become alarmed if I had only known why they were so disturbed." In this case, the "Much Ado About Nothing" came near resulting in a damage suit.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

NO. XXXV. THE NEWER INTERPRETATION OF THE GASTRIC PAIN IN CHRONIC ULCER *

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The precise nature of the characteristic pain of peptic ulcer is a matter of some dispute. It is generally assumed to be dependent on and to bear a direct relation to gastric acidity. This view has seemed especially plausible in view of the alleviation of the pain by alkalies. Many textbooks and teachers state that the pain is due to direct irritation of the sensory nerve endings at the base of the ulcer by the acid or by mechanical means by invoking peristalsis. Still others believe the distress is caused by the acid bolus impinging against the pylorus.

HAS THE STOMACH PAIN NERVES?

Before discussing the irritating action of acidity or motility, we must consider the existing confusion regarding visceral pain in general and gastric pain in particular. The situation is well discussed in Hertz's work.[1] From observations in a case of gastric fistula, Carlson[2] concludes that the sensation of pain cannot be produced from the normal mucosa by any stimulation confined to the mucosa itself. Lennander[3] con-

* Dr. Ginsburg died March 9, 1916, during the course of the research for which he was most responsible.

1. Hertz: Sensibility of the Alimentary Tract, London, 1911, pp. 47-54.
2. Carlson, A. J.: Am. Jour. Physiol., xxxvi, 154.
3. Lennander, K. G.: Abdominal Pain, THE JOURNAL A. M. A., Sept. 7, 1907, p. 836.

cluded from his researches that only the parietal peritoneum is sensitive to pain and that visceral pain is due to stimulation of the parietal peritoneum by pressure, inflammation or traction on the mesentery. The conclusiveness of these experiments was overthrown by Kast and Meltzer,[4] who pointed out the fallacy of employing cocain infiltration. They demonstrated that local infiltration with cocain abolishes all sensation even after electrical stimulation, that the same amount of cocain injected into the leg would produce the same results, and that, therefore, systemic absorption of the drug is sufficient to abolish visceral sensations. Furthermore, they proved that there is actual pain sensation and that the sensitivity of the inflamed organ is still greater. These results were confirmed by Ritter.[5] The slight degree of sensitiveness of the viscera as compared with the skin is due to the smaller number of afferent nerves, as shown by Langley.[6] We may assume that the stomach has pain nerves. The question arises, Does the acid irritating the ulcer cause pain?

THE RELATION OF ACIDITY TO PAIN

In normal stomachs, injection of weak acids causes no pain. This has been shown repeatedly. Lowenthal[7] gave 250 c.c. of hydrochloric acid by tube and left it in one minute. With 0.3 per cent. no sensation was produced, while with 0.5 per cent. an occasional subject would experience a warm sensation. Hertz, Cook and Schlesinger[8] found that 0.5 per cent. hydrochloric acid causes no sensation in normal individuals. Schmidt,[9] using from 0.5 to 2 per cent. acid through gastrostomy openings of the empty stomach in three cases failed to produce symptoms. Boring,[10] with the

4. Kast and Meltzer: Med. Rec., New York, 1906, lxx, 1017.
5. Ritter: Central. f. Chir., 1908, xxxv, 609.
6. Langley: Brain, 1903, xxvi, 23.
7. Lowenthal: Berl. klin. Wchnschr., 1892, xxix, 1188.
8. Hertz, Cook and Schlesinger: Jour. Physiol., 1908, xxxvii, 481.
9. Schmidt, J. E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, xix, 278.
10. Boring: Sensations of the Alimentary Tract, Am. Jour. Psychol., xxvi, 48.

enormous strength of acid of 5 per cent., experienced a sensation very much "like the ache of hunger."

In cases of ulcer, the most varied results have been reported. Heinecke and Van Selms[11] produced pain in four cases of ulcer by administering from 0.1 to 0.4 per cent. acid by tube. Bonminger[12] states that 100 c.c. of 0.36 per cent. hydrochloric acid always produces a violent pain in ulcer which is temporarily relieved by milk. On the other hand, Hertz[13] reports that in six cases of ulcer whose diagnoses were confirmed by operation, 4 ounces of 0.5 per cent. hydrochloric acid produced no sensation even when pepsin was added. Lowenthal's results agreed with those of Hertz. These results are especially valuable since it is doubtful whether the free acidity of the gastric contents ever exceeds this concentration. It is well known that hyperacidity symptoms may be present with normal acid values[14] and even in cases of achylia.[15] Boas and others report cases in which persons obtain relief from soda who have no increased acid values.[16] Bolton,[17] also, states that pain has little or no relation to acidity inasmuch as pain is relieved by food whether the gastric contents are acid or not. Hyperacidity may remain when pain is relieved by treatment.[18] Some of these diametrically opposed results may perhaps be explained by the suggestion that they depend on the emptying time and the condition of the pylorus, and that the acid is neutralized by the bile and intestinal juices. We may also assume that the stomach in some of these cases presents a hyperesthesia for acid. However, it appears sufficiently clear from such a great diversity and absolute disagreement of findings that acidity alone cannot be the cause of pain.

11. Heinecke and Van Selms: Arch. d. mal. de l'app. digestif, 1908, ii, 467.
12. Bonminger: Berl. klin. Wchnschr., xlv, Sec. 1, p. 396.
13. Hertz: Sensibility of the Alimentary Tract, p. 57.
14. Talma: Ztschr. f. klin. Med., 1884, vii, 407.
15. Einhorn: Arch. f. Verdauungskr., vii, 23. Kuttner, L.: Ztschr. f. klin. Med., liii, 1. Leo: Therap. d. Gegenw., December, 1904.
16. Boas, I.: Diagnostik und Therapie der Magenkrankheit, Ed. 6, Leipzig, 1911, p. 355.
17. Bolton: Ulcer of the Stomach, London, 1913, p. 149.
18. Hertz: Sensibility of the Alimentary Tract, p. 56.

TENSION THE ADEQUATE STIMULUS

More recent advances in stomach physiology tend to the conclusion that the adequate stimulus for pain in hollow viscera like the stomach is tension. Hertz pointed out that observers of gastric sensibility overlooked this factor. He believes that tension is the only cause of true visceral pain, and demonstrated that inflation of the stomach leads to a sensation of fulness when the intragastric pressure is from 12 to 15 mm. of mercury.[19] Actual pain results if distention is produced rapidly. The tension factor in stomach contractions can well be demonstrated. Fluoroscopic examination discloses in even the normal fasting stomach peristaltic waves beginning about the middle of the body, growing deeper as they reach the pylorus, contracting the cavity. It is easy to understand that the exaggerated peristalsis in the hypertonic organ causes an excessive intragastric pressure, and that the muscular tension in the irritable condition causes pain. Moynihan[20] now believes that the pain is not so much due to the chemical changes in the chyme as the alterations of the muscular activities of the stomach and duodenum which may be stimulated by the chemical factors. Boas[21] also suggests that gastric pain and tenderness occur only at the time of emptying and are rapidly relieved by food taking, due, as he says, to abnormally strong pyloric contractions occurring stronger at the end of digestion. Bayliss and Starling[22] state that a wave occurs in one part of the alimentary tract while the part below should relax. Organic diseases or spasm from reflex irritation may prevent it so that the segment between the peristaltic contractions and the obstruction is subjected to a steadily increasing tension.

19. Hertz: Sensibility of the Alimentary Tract, pp. 47, 54. Boring: Sensations of the Alimentary Tract, p. 45.
20. Moynihan: Duodenal Ulcer, 1912, Ed. 2, Philadelphia and London.
21. Boas, I.: Diagnostik und Therapie der Magenkrankheit, Ed. 6, Leipzig, 1911, p. 616.
22. Bayliss and Starling: Recent Advances in the Physiology of Digestion, London, 1906.

With tension as the immediate cause of pain an explanation of the relation of acidity is offered from a consideration of the work of Edelman[23] and Ducchesi.[24] They find that hydrochloric acid stimulates peristalsis. Such action would, of course, tend to increase intragastric tension. Carlson[25] does not find this to be true in normal man, and we have not found it so in the few cases in which we used it in ulcer. Cannon finds peristalsis and tonus even when the stomach contents are alkaline.[26] Hertz[18] offers another solution which might reconcile the relation of acidity and pain on the ultimate basis of tension. Excess acid passed into the duodenum prevents relaxation of the pylorus, permitting an increase in intragastric tension. The effect of acidity in the duodenum, of course, will depend on the alkalinity of the duodenal juices. Hertz also suggests that there are more nerve endings in the deeper structures of the stomach wall when exposed by ulcer and that these are stimulated by acid, alcohol and coarse foods, causing increased peristalsis and inhibition of pyloric relaxation. This view has been confirmed by paralysis of the nerve endings with orthoform. His Roentgen-ray examinations show that duodenal ulcer is accompanied by increased gastric tonus. Hyperacidity may then cause pain indirectly in many ways, causing hyperperistalsis and prevention of pyloric relaxation with usually intensified gastric tonus. In this way it effects a true pyloric syndrome which may be aggravated if there is also a hyperesthesia toward acid. It has been emphasized that chronic appendicitis and gallbladder disease are often associated with hyperperistalsis and hyperacidity, which may explain the epigastric pain so frequently found in these conditions. Cannon and Murphy[27] demonstrated that injury of the intestines causes inhibition of

23. Edelman: Dissert. (Russian); abstr., Jahresb. ü. d. Fortschr. d. Physiol., xv, 119.
24. Ducchesi: Arch. p. le Sc. Med., 1897, xxi, 154.
25. Carlson: Am. Jour. Physiol., xxxii, 249.
26. Cannon: Am. Jour. Physiol., 1907, xx, 299.
27. Cannon and Murphy: Ann. Surg., 1906, xliii, 512.

pyloric relaxation which may lead to hypertonus. The pylorus may be felt as a tumor in operating for the lesion. All these considerations tend to prove that the pain in gastric ulcer is not primarily a matter of mere acidity but a condition due to motor activity of the stomach manifested by hypertonus, hyperperistalsis and pylorospasm, often with a condition of hyperesthesia.

HUNGER AND TENSION

The mechanism of hunger has been quite definitely established through the work of Carlson[28] and Cannon and Washburn.[29] They studied the activity of the empty stomach by means of a delicate balloon attached to a manometer which registered the changes in intragastric pressure due to contractions of the stomach. Boldireff,[30] using dogs, was the first to apply this method. He found that the whole alimentary tract had a periodic activity when not digesting. He found periods lasting from twenty to thirty minutes characterized by rhythmic contractions ten to twenty in number followed by a rest of one half to two hours and repeated. He believed that hunger caused the contractions. Cannon and Washburn extended their observations to man. They found that the strong contractions of the stomach were accompanied by the sensation of the hunger pang. While the tracing was taken the observed, who could not see the results, was asked to press a key when the sensation was noted. Invariably, the feeling occurred after the powerful contractions had reached their height. The feeling disappeared when the contractions ceased, and the contractions could not be controlled by the observed. Carlson elaborated extensively on these results, using a gastric fistula man in part of the work. He found a fairly close correspondence between the degree of hunger and the strength of the contractions, and that the recognition of this condition as hunger

28. Carlson: Am. Jour. Physiol., xxxi, 151, 175, 212, 318; xxxii, 245, 369.
29. Cannon and Washburn: Am. Jour. Physiol., 1912, xxix, 441.
30. Boldireff: Arch. biol. de St. Petersburg, 1905, xi, 1.

depends also on the rapidity of the contraction phase.[31] It was reported as early as 1898 that when the stomach empties itself the midregion becomes narrowed to a tubular portion as seen by the x-ray.[32] Waves then originate as tonic rings separating the tube from the rounded cardiac sac. These rings form depressions seen in the x-ray plate. A more recent Roentgen ray examination of a normal fasting stomach with simultaneous record of the hunger contractions by means of a bismuth coated balloon was made by Rogers and Hardt.[33] Fluoroscopic examination, which the authors had the privilege of witnessing, disclosed peristaltic waves beginning about the middle of the body growing deeper as they reached the pylorus. There were frequently as many as three constricting rings passing over the stomach at one time. As these occurred the tracing registered extremely high hunger contractions, and the subject invariably pressed the key recording the hunger pang accompanying the contractions. As Carlson states, the afferent nerves of the mucosa are not primarily concerned in the genesis of hunger. Hunger seems to be produced by contractions only, that is, by stimulation of the nerves in the muscularis.[34]

THE PRESENT PROBLEM

It has probably already occurred that there is a significant similarity between the condition of the stomach in hunger and in ulcer. The difference appears to be largely a matter of degree of sensitivity caused perhaps by hyperactivity and hyperesthesia. The situation admirably illustrates that the laboratory man is justified in censuring the clinician who only considers those things pertinent which manifest clinical symptoms. For as the laboratory worker points out, the same condition acting in two cases may produce clinical symptoms in one and none in the other. That the

31. Carlson: Am. Jour. Physiol., xxxi, 180.
32. Kaestle, Rieder and Rosenthal: Arch. Roentgen Ray, 1910, xv, 21, 24.
33. Rogers and Hardt: Am. Jour. Physiol., xxxviii, 274.
34. Carlson: Am. Jour. Physiol. xxxi, 188.

hunger contractions of the normal stomach have a direct bearing on the pain in ulcer might have been anticipated from the statements of Hertz[35] that "the same mechanism producing pain gives fulness: this latter sensation occurs for months before pain"; and Moynihan,[36] that "the characteristic hunger pain of duodenal ulcer is preceded and accompanied by sensations of fulness and hunger." From the close analogy between the state of hunger and the more plausible view that ulcer pain is due to tension, it was thought that a study of the conditions by the balloon method would yield a concrete demonstration of the tension in the one case and prove its similarity to hunger contractions in the other.

METHOD AND RESULTS

Ten cases under the care of one of us (W. W. H.) at the Cook County and Michael Reese hospitals diagnosed clinically as peptic ulcer were examined. Two tubes, each about 5 mm. in diameter, were prepared. To one was attached the balloon. The other was a modified Rehfuss tube made by enclosing a piece of lead at the very end and perforating the tube for about 3 cm. above. It was expected that the weight would carry the tube to the dependent parts so that the contents might be aspirated from time to time. The two tubes were swallowed at once. The balloon tubing was connected with a T tube through which the balloon was distended and a chloroform manometer. A cork float on the column of chloroform supported a rod to which was attached an indicator to write on a slowly moving drum. The aspiration tube was connected with a wash bottle holding about 300 c.c. By suction through the shorter arm of the bottle the contents of the stomach could be quickly aspirated. By the same arrangement various solutions could be rapidly and easily forced into the stomach without the knowledge of the observed. The

35. Hertz: Sensibility of the Alimentary Tract, p. 59.
36. Moynihan: Duodenal Ulcer, p. 101.

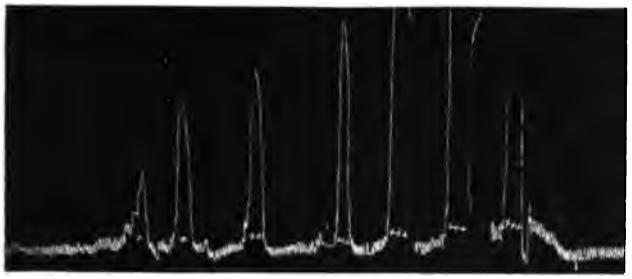

Fig. 1.—Case of gastric ulcer, showing that degree of pain varies with strength of contractions.

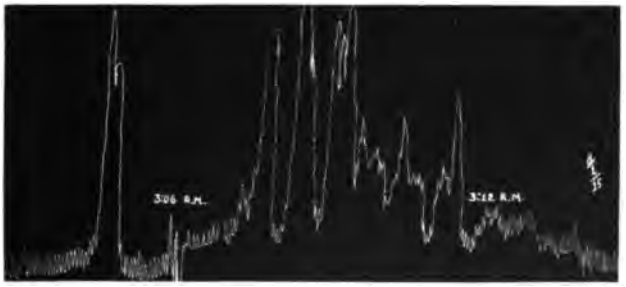

Fig. 2.—Case of gastric ulcer, showing period of tetany.

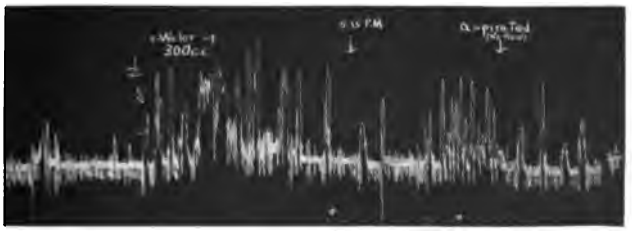

Fig. 3.—Immediate effect of rapidly injecting 300 c.c. of tap water.

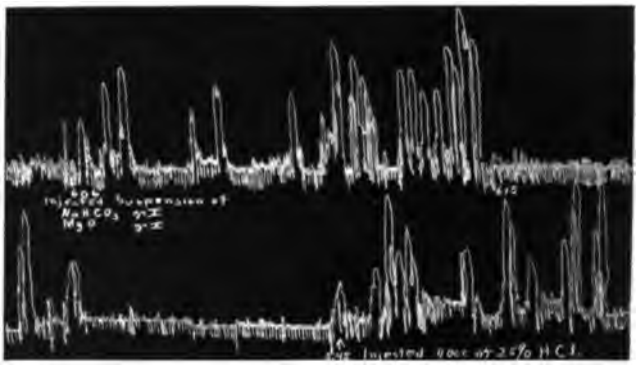

Fig. 4.—Injection of 40 c.c. of 2.5 per cent. hydrochloric acid giving fairly vigorous contractions lasting thirty minutes which were abruptly terminated nine minutes after the administration of an aqueous suspen sion of magnesium oxid and soda, 10 grains of each.

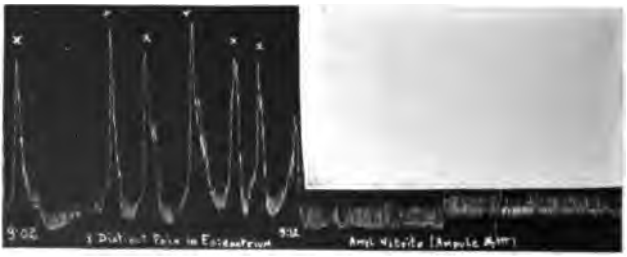

Fig. 5.—Inhalation of a 3 minim pearl of amyl nitrite absolutely abolished the painful stomach contractions, resulting in a state of flaccidity which persisted for four hours.

Fig. 6.—Injection of 15 minims of pituitary extract subcutaneously; contractions began in ten minutes, lasted thirty-five minutes, and were followed by a long period of inactivity.

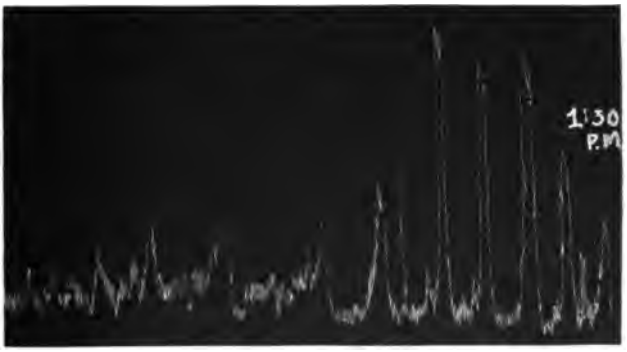

Fig. 7.—Case of gallstones, showing the onset of contractions, which were accompanied by pain.

subject was at rest in bed while the tracings and manipulations were made, and usually fell asleep, aroused occasionally by distress. Observations lasted as a rule from two to four hours, and in one case a continuous twenty-four hour tracing was obtained.

REPORT OF CASE

P. S., man, aged 27, was admitted to the Michael Reese Hospital, July 19, 1915, complaining of pain in the epigastrium coming on about one hour after eating. The distress had been growing worse for the preceding two years. It was not present in any other part of the abdomen, and was not referred posteriorly. It was aggravated by food of any description and by drinking, and was more severe about an hour after eating. It was relieved by pressure over the abdomen and by vomiting. Nausea and vomiting began with the onset of the condition, and occurred about one-half to one hour after meals. Vomiting sometimes occurred after water. There was a sour taste and odor and a burning sensation on vomiting. He had noticed a small amount of blood in the vomitus only once, seven months before entering the hospital. Eructations occurred more or less constantly all day and caused a sour taste in the mouth and burning in the throat. He had never noticed blood in the stools. He had lost forty pounds in weight since the beginning of his illness.

Examination showed marked visible peristalsis extending from the left upper to the right lower abdomen. This region was distended and somewhat rigid. After an Ewald meal, 750 c.c. was recovered. Between 1,000 and 2,000 c.c. was commonly recovered on aspiration of the stomach at different times. The free acidity averaged about 28 and the total about 60. Fluoroscopic examination showed a large stomach displaced downward. No cap was seen. A thin line of bismuth was seen to pass. Otherwise the pyloric end was very broad and sharply cut off from the rest of the organ. After thirty hours considerable bismuth still remained in the stomach.

A diagnosis was made of cicatricial pyloric narrowing following gastric ulcer with gastroptosis. Tracings taken from this case showed extremely marked contractions accompanied by visible peristalsis usually (Fig. 1). Periods of tetany were quite frequent (Fig. 2).

From repeated observations on ordinary cases, the regular picture of the normal hunger contractions was obtained, but it was striking that the contractions were not more severe and of approximately the same excur-

sion as the normal hunger picture. In hunger the sensation is interpreted as a pang; in ulcer, as a pain. With the onset of the strong contractions shown in our tracings, the patients complained of symptoms varying in interpretation from a feeling of fulness and tightness to severe epigastric pain. In several cases the patient was aroused from sleep with the complaint of pain. The sensation nearly always came on when the contractions had reached their height. In one case at the height of the contraction the patient vomited. Between the periods of activity the patient registered no complaint. These contractions could not be seen and were not understood by the patients. While the record was taken, various substances were injected into the stomach by the arrangement described. In one case 300 c.c. of milk caused transitory contractions. The same was found true by an equal quantity of tap water (Fig. 3). This may have been caused by the rapid introduction of the liquids causing distention.[37] Hydrochloric acid in strengths of 0.5 and 1 per cent. caused little or no effect on the contractions and no effect on the sensations. In one case 40 c.c. of 2.5 per cent. acid caused a period of rather vigorous contractions lasting one-half hour and terminating abruptly nine minutes after administering a suspension containing 10 grains each of soda and magnesium oxid (Fig. 4). In another single case 70 c.c. of 5 per cent. acid caused intense burning, and the patient vomited balloon and tubes. Administration of soda immediately relieved him, and he ate his luncheon five minutes later entirely comfortable. The subjective sensations caused by 2.5 per cent. acid could not be relied on since the subject was very ignorant and untractable. One per cent. solutions of soda in 300 c.c. quantities caused no noticeable effect. A 3 minim pearl of amyl nitrite was given by inhalation in one case. The patient became extremely faint,

37. Carlson: Am. Jour. Physiol. xxxii, 248.

and the strong contractions which had been registering absolutely ceased, to be followed by a period of absolute flaccidity which lasted four hours (Fig. 5). While a tracing was taken of a quiescent stomach, 15 minims of pituitary extract was injected subcutaneously into the arm. In ten minutes well marked hunger contractions set in, even displaying short periods of tetany. This lasted for thirty-five minutes, when the stomach again became flaccid (Fig. 6). In a case of gallbladder disease in which fluoroscopic examination of the stomach showed no abnormality, strong contractions occurred with pain, closely resembling the results in ulcer (Fig. 7).

CONCLUSIONS

1. The finding of strong contractions of the stomach accompanying the pain of gastric ulcer seems to confirm the idea that pain is due to tension.

2. The marked hunger contractions cause pain in a hyperirritable condition of the stomach by increasing intragastric pressure.

3. The conception that gastric pain is due to tension will explain many obscure conditions simulating gastric ulcer, viz., achylia gastrica, chronic appendicitis and gallbladder disease.

4. Hyperacidity, alone, may be a factor by reflexly causing hypertonus, hyperperistalsis and pylorospasm, allowing greater tension to be produced.

5. The subjective relief of pain by alkalies does not necessarily prove that acid is the cause of pain, but may be interpreted on the basis that alkalies prevent the development of pain producing hypertonus by neutralizing the causative factor of such hypertonus, i. e., acid.

6. Pituitary extract stimulates contractions, as is to be expected from its property of stimulating smooth muscle.

7. Amyl nitrite in the case reported abolished the contractions, probably by stimulating the inhibitory nerves or by lessening the reflex excitability.

8. From the results obtained, hydrochloric acid in the strength that it may occur in the stomach (about 0.5 per cent.) causes no appreciable effect. The authors do not feel justified in drawing final conclusions regarding the effect of acidity until more cases are studied whose emptying time and condition of the pylorus is more thoroughly observed.

We wish to thank Dr. A. J. Carlson for his valuable suggestions and Drs. J. Meyer and J. R. Rupp for their kind assistance in a part of this work.

CARBOHYDRATE RESTRICTION IN THE MEDICAL TREATMENT OF GASTRIC HYPERACIDITY AND ULCER

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Gastric hyperacidity forms a very considerable part of the symptoms of dyspepsia which the physician is called on to treat. It may exist (1) as part of the syndrome associated with prolapsed viscera and the attendant neurasthenic state coupled with a faulty dietary; or (2) as a result of reflex disturbance from some neighboring abdominal organ, such as the gall-bladder or appendix, or (3) as a result of faulty habits of mastication and the choice of appropriate food.

Although easy of diagnosis, the cause of the disturbance is not always so easy to fathom. The chief factor concerns the remote results of chronic hyperacidity. It is safe to say, in the present state of our information, that ulceration in stomach or duodenum rarely occurs without long standing hyperacidity. Moreover, the medical treatment and cure applicable in a large percentage of ulcer cases depends to a great degree on neutralization of the acid secretions by the administration of appropriate food and sufficient alkali. This has been amply demonstrated by Sippy.[1]

Of the many explanations as to the cause of chronic ulcer offered since the day of Cruveilhier and Rokitansky, but few have stood the test of time. The corrosive action of hyperacid chyme, coupled with factors which render the gastric mucosa more susceptible to digestion, such as metastatic emboli, local thrombosis, trauma, infection or a combination of these conditions, serves as the usual explanation.

1. Sippy, B. W.: Gastric and Duodenal Ulcer; Medical Cure by an Effective Removal of Gastric Juice Corrosion, THE JOURNAL A. M. A., May 15, 1915, p. 1625.

In the production of ulcer there may be mentioned the experimental ligature of arteries supplying certain portions of the gastric wall; the addition of bacterial infection to acutely traumatized areas of gastric mucosa; the local injection of substances acting as chemical irritants; the production of general anemia with the addition of local irritants; and lastly, by artificial occlusion of the pylorus with resulting motor insufficiency after acute ulceration has been produced. Although acute ulceration can be readily produced by these means, the majority heal readily and do not become chronic. In other words, the tendency to heal is rarely absent in experimentally produced lesions.

In patients manifesting ulcer symptoms the same tendency is present, providing the cause is sought for and relieved and the ulcer area protected from the action of acid chyme by properly selected food frequently administered and by doses of the alkalies adequate to secure neutralization of the gastric juice. As Pawlow[2] has stated: "In clinical, pharmacologic and physiologic textbooks, it is stated that the alkalin salts of sodium promote a flow of gastric juice. We may look in vain, however, for any experimental foundation to support this doctrine." In fact, alkalies have been shown to exert a distinct inhibitory influence on the gastric glands quite distinct from their neutralizing effects on acids already present. In most patients a combination of causative factors can usually be found. The first aim, of course, should be to correct the cause.

Of the first group mentioned above, prolapse of the viscera, including the stomach, is, in my experience, frequently associated with the hypersecretion of acid chyme. If with this factor there is also associated a faulty dietary, especially of the carbohydrate elements, favoring bacterial decomposition within the organ, and if, because of the chronicity of the prolapsus, spasm and motor insufficiency has occurred, the conditions are favorable to the train of symptoms

2. Pawlow: The Work of the Digestive Glands, London, 1902.

which we have come to recognize as chronic ulcer. Our first aim should be, therefore, to support the viscera, including the stomach, by proper appliances or belts in as nearly a normal position as is possible under the circumstances, and second, to restrict or limit the intake of carbohydrate foods in order to lessen bacterial fermentation and the elaboration of organic acids. As is well known, hypomotility favors bacterial fermentation within the stomach.

Enough experience has accumulated to show the importance of attention to septic foci about the teeth and tonsils. The organisms daily swallowed by patients with septic mouths, septic tonsillar crypts and nasal sinuses, may contribute materially to bacterial fermentation of the carbohydrate elements usually present in excess in a mixed meal, if not, as believed by many investigators, to actual ulceration. In this connection it has always been a source of wonder to me why more patients with septic mouths, from extensive pyorrhea did not manifest stomach symptoms. Alveolar abscesses may serve as foci of infection, although it is difficult to understand the method of bacterial metastasis and the supposed selective affinity for certain tissues.

Of the second group in which reflex disturbance from some neighboring organ may be a factor of importance, my records of the past ten years have shown that in approximately 50 per cent. of the patients manifesting symptoms of hyperacidity and ulcer various causes have appeared to be operative. In order of frequency these have been coincidental gallbladder disease, stones or adhesions; chronic obliteration, twist or adhesions involving the appendix; uterine malposition or adhesions; tubal disease; renal or ureteral stone and abdominal hernias. On the other hand, many patients with such conditions do not complain of disturbed digestion, while many others with no secretory disturbance complain of gastric distress. Syphilitic ulcer has been excluded from these figures,

for when it has existed the cure has resulted from the employment of specific measures in addition to those applicable to the treatment of simple septic ulcer.

In the third group there occurs apparently an increasingly large number of patients in which the disturbing causative factor appears to be a tendency to an abnormal consumption of carbohydrates, coupled with poor salivation as a result of hurried and faulty mastication due to poor teeth. The monosaccharids, such as dextrose, levulose and galactose, are fermented by yeast into alcohol and carbonic acid. Lactic acid is also formed by the action of the *Bacterium lactis*. The disaccharids, such as saccharose, maltose and lactose, are not fermented by yeast, but may be broken up into lactic acid by the *B. lactis* or butyric acid by the *B. butyricum* of Pasteur, or the micrococci of butyric fermentation discovered by Fitz. Of the polysaccharids, starch is likewise subject to bacterial fermentation with the formation of organic acids.

For years the idea has held ground that an excessive protein diet was a factor of importance in the causation of hyperchlorhydria. There can be no doubt that the symptoms of such a condition and that of ulcer are sometimes found in patients who have been excessive meat eaters. For this reason, and certain experimental data, the belief has been prevalent that meat extractives caused the hypersecretion of hydrochloric acid through acting as chemical excitants, and as such should be avoided in the treatment of gastric hyperacidity. This is a matter of relative importance only. Regardless of what experiment may show in animals, the deductions when applied to patients must justify themselves by results. It may be mentioned that foods rich in albumin bind larger quantities of hydrochloric acid than carbohydrate foods. This holds true in experiment on normal animals and is probably true under pathologic conditions in man.

The tendency of the past few years has been toward the restriction of meats and albuminous foods in the

treatment of hyperchlorhydria and ulcer and the substitution therefor of carbohydrate foods. This belief has gained ground largely from the work of Pawlow, who published his experiments in 1902. He showed that in dogs the quantity of gastric juice secreted from hour to hour was greater after meat than after bread and milk. He likewise showed that the acidity of juice secreted after meat was greater (0.56 per cent.) than after bread (0.46 per cent.). The juice secreted after bread contained, however, more ferment than that secreted after meat. The point should be noted that the hourly intensity of gland work was much less with bread, which would mean that the time required for the digestion of its protein constituents was longer and that the duration of gastric secretion was correspondingly protracted. It seems, therefore, in the type of carbohydrate digestion manifested by bread and cereals, that there exists a slightly lower hydrochloric acidity, but a more protracted secretion. Since there is no provision in the stomach for carbohydrate digestion, it has seemed plausible, in this day of excessive sugar consumption, that this common dietetic fault might be responsible for the altered gastric secretion found in a large majority of patients suffering with hyperacidity, pyloric spasm and ulcer.

I am indebted to L. M. Estabrook, Chief of Bureau of Crop Estimates, U. S. Department of Agriculture, for Table 1, published in an earlier article,[3] which shows the great increase in sugar consumption for the period 1871 to 1911 in the United States, United Kingdom, France and Germany. The per capita consumption[4] has been computed by adding the produc-

3. Stone, W. J.: The Carbohydrate Factor in the Causation and Treatment of Hyperacidity and Ulcer, THE JOURNAL A. M. A., Jan. 29, 1916, p. 324.

4. Consumption includes all uses in households, in factories and elsewhere. Figures for the United States and the United Kingdom refer partly to raw and partly to refined sugar; for France, figures for 1871, 1881, and 1891 refer to raw, and for 1901 and 1911 to refined sugar; for Germany, figures for 1871 and 1881 refer to raw, and other figures to refined sugar. This table was compiled from the Statistical Abstract of the United States, Statistical Abstract of the United Kingdom, Annuaire Statisque (France), and Statistiche Jahrbuch für das deutsche Reich (Germany). Those interested may also consult Bull. U. S. Dept. Agriculture, No. 66, March 10, 1914.

tion of a given country to its imports and subtracting its exports.

The point is made that the moderate consumption of carbohydrates under normal digestive conditions is a different matter than excessive consumption when hyperchlorhydria is present. In patients with pyloric spasm or ulcer the excess is required to remain in the stomach during the process of protein digestion of the other constituents of a mixed meal, with the result that bacterial fermentation follows and the symptoms of so-called amylaceous dyspepsia become evident. As

TABLE 1.—ESTIMATED AVERAGE PER CAPITA CONSUMPTION OF SUGAR IN FOUR IMPORTANT COUNTRIES

Year	United States,* Pounds	United Kingdom† (Net Imports), Pounds	France,† Pounds	Germany,‡ Pounds
1871	36	44	17	12§
1881	43	64	22	15
1891	61	78	26	21
1901	71	91	24	27
1911	77	92	39	42
1912	82.4			

* For years ending June 30.
† For years ending December 31.
‡ For years ending August 31.
§ For 1872.

is well known patients with hyperacidity complain of their inability to digest starchy foods. Their distress appears to be due primarily, not to the hydrochloric acid content of the stomach, but to the bacterial elaboration of organic acids from carbohydrate fermentation. Later in the process of gastric digestion, usually after one hour, hypersecretion of hydrochloric acid occurs as a result, I have believed, of the stimulating effect of such organic acids as butyric, lactic, acetic and proprionic. If either the Rehfuss, Einhorn or simple duodenal small tube with the catheter end is employed after a hastily swallowed bulky carbohydrate meal and the secretion removed at five to ten minute intervals the curve of hydrochloric acid does not reach its maximum as a rule until after the expira-

tion of one hour, while the organic acids become evident within a much shorter interval. Pawlow[2] has shown that butyric acid strongly excites gastric secretion. Although my experience with the test meal advocated by Skaller[5] is limited, it has much to commend it. It consists of 5 gm. of Liebig's beef extract in 200 c.c. of water. It is more palatable and gives a truer picture of gastric secretion than the Ewald meal.

Clinically, patients with hyperacidity, delayed motility and ulcer do better when their intake of carbohydrate foods is lessened. Deeks[6] called attention to this in 1912. Although I cannot subscribe to all the restrictions imposed by him, I am convinced that excess of carbohydrates is a common dietetic error with such patients. I am also convinced that restriction generally to those articles of food which do not contain more than from 10 to 15 per cent. carbohydrates, with small additions of food which contain more than 20 per cent., such as bread and potato, together with sufficient alkali to limit the secretion of hydrochloric acid, has given better results than heretofore obtained. The following general diet list in hyperacidity I have found useful, articles from which may be omitted if found necessary in any given case.

Proteins and Fats.—Soft boiled or poached eggs, omelette, broiled or baked fish, bacon, chicken, oyster or clam broth, custard (use slight amount of sugar), butter, milk and cream, cream cheese, olive oil, tea.

Five Per Cent. Carbohydrates (Fodder-Vegetables and Fruits).—Asparagus, cauliflower, water cress, spinach, eggplant, lettuce, beet or dandelion greens, string beans, olives, grape fruit pulp.

Ten Per Cent. Carbohydrates (Fodder-Vegetables, Fruits and Nuts).—Onions (boiled), squash, turnips, carrots, beets, lemon juice (one teaspoonful with one ounce olive oil twice daily as salad dressing), orange juice and pulp, peaches, watermelon, cantaloupe or musk melon, hickory nuts, filberts.

Fifteen Per Cent. Carbohydrates (Fodder-Vegetables, Fruits and Nuts).—Green peas, parsnips, canned Lima beans, baked apple (pulp), pears, pecans, almonds, English walnuts.

5. Skaller: Berl. klin. wchnschr., 1915, lii, 105.
6. Deeks, W. E.: New York Med. Jour., Nov. 30, 1912.

The patient may take daily in addition, one potato, three slices toast, one portion breakfast cereal or rice, purée of pea, corn ("Kornlet") or spinach.

Avoid excess sugar in above foods, candy, syrups, condiment sauces, pickles, green corn, tomato, cornstarch, macaroni, spaghetti, bread, crackers, cocoa, chocolate, coffee and vinegar.

In addition the patient is requested to take one glass of milk between meals and at bedtime. After each meal and after each glass of milk between meals, a powder consisting of heavy magnesium oxid, sodium bicarbonate and bismuth subcarbonate is to be taken in from one half to one teaspoonful doses in one third glass of water. If evidences of hypersecretion exist the powder is given every two hours, regardless of the feedings, between 7 a. m. and 10 p. m., with an additional glass of milk and a dose of the powder should the patient awake during the night. By this plan, the details of which were more generally stated in the previously published article,[3] relief is soon obtained, the evidences of pyloric spasm and food retention are decreased and the pyrosis and hunger pain soon disappear due to the lessened gastric secretion and hunger contractions. It is, of course, difficult to rid the stomach of the bacteria of organic acid fermentation. If the organic acids persist, as evidenced by flatulence and pyrosis, gastric lavage may be used once daily one hour before the principal meal. A liter of a solution of salicylate acid 1 to 1,000 is well adapted for this purpose.

In the treatment of ulcer it is necessary to secure absolute rest, usually in the hospital. Patients treated at home are usually unable to secure the rest and nursing cooperation necessary to the best results. In other words, they, as a rule, cannot be made while at home to attend strictly enough to the business of getting well. Although the details of the ulcer diet here given differ somewhat from the plans advocated by Lenhartz and by Sippy, the essentials are the same in so far as the attempt is made to control the supersecretion, to limit the secretion of hydrochloric acid and by fre-

quent feedings and sufficiently large doses of the alkalies to prevent continuous local irritation of the ulcer area. This plan has been used with slight modifications since 1913 with good results in prepyloric, pyloric and duodenal ulcers.

Remarks on Treatment.—Neutral sodium citrate, 3 grains to each ounce of milk may be given to prevent curd formation in the stomach.

TABLE 2.—ULCER FEEDING SCHEDULE

Day	Diet and Frequency	Time	
		A. M.	P. M.
1st	Milk, 2 ounces, every 2 hours	6	8
	Albumin water, 3 ounces, every 2 hours	7	9
2d	Milk, 2 ounces, cream, 1 ounce, every 2 hrs.	6	8
	Albumin water, 3 ounces, every 2 hours	7	9
3d	Milk and cream as above, every 2 hours	6	8
	Albumin water, as above, every 2 hours	7	9
	One soft boiled egg, with feeding at	7	7
4th	Milk and cream as above	6	8
	Albumin water as above	7	9
	One egg as above, with feeding at	7	7
	Soft, well cooked cereal, 3 ounces, with feeding at	8	2
5th	Milk and cream as above	6	8
	Albumin water as above	7	9
	One egg as above, with feeding at	7	1 and 7
	Cereal as above with feeding at	8	2
	Purée, 3 ounces, with feeding at	12 M.	6
6th	Milk and cream as above	6	8
	Albumin water as above	7	9
	One egg with 2 slices bacon, with feeding at	7	1 and 7
	Cereal as above, with feeding at	8	2 and 8
	Purée as above, with feeding at	12 M.	6
7th	Repeat above and 3 ounces broth, with feeding at	10	4
8th	Same as seventh and broth, with feeding at	10	4 and 10
9th to 14th	Same as eighth and ½ slice toast with three feedings. Custard, 3 ounces, may be substituted for one or two milk or albumin water feedings if desired		

Give ½ to 1 teaspoonful of alkaline powder (usually magnesium oxid 5, bismuth subcarbonate 5, sodium bicarbonate 20) after each feeding at 6 a. m. and 10 p. m.

The albumin water contains white of one egg flavored with orange or lemon juice, with no sugar.

If a taste of the milk remains in the mouth, use a weak borax mouth wash after each milk feeding.

If patient has been starved, give proctoclysis daily, by drop method, of 1 quart tap water containing 1 ounce dextrose.

Butter may be added to cereal or egg if desired.

Avoid much sugar in preparation of custard.

Purée refers to pea, spinach or corn ("Kornlet").
Cereal refers to Cream of Wheat, Ralston's, boiled rice or Farina (measured after cooking).
Broth refers to chicken, oyster or clam.
Bacon should be fried crisp.
If retention of food exists lavage stomach one hour after last feeding at night.
Take weight of patient every alternate day.

It is obvious that in extensive ulcer areas involving the lesser or greater curvature with hour-glass constriction, a medical cure may not be secured; but since most of these are the result of a spasmodic indrawing of the curvature opposite the ulcer, relief is many times as adequately secured by the medical cure as by surgical intervention, since the spasm diminishes in direct ratio to the protection given the ulcer. This may not be true in chronic ulcers with undermined edges or of course in those with definite scar tissue formation. It has been surprising, nevertheless, to note the relief obtained in those patients manifesting symptoms of long-standing pyloric obstruction in whom scar tissue contraction was suspected but which, from the results obtained, could have been nothing more than edematous infiltration of the pyloric ring incidental to spasm.

Gastro-enterostomy, so frequently performed in such patients, does not give any more adequate results. In fact, unless performed for the relief of perigastric adhesions or perigastric abscess, the result of an earlier walled-off perforation, or for severe hemorrhage, which is rarely necessary, or following partial resection or excision of an area suspected of being carcinomatous, the operation will probably be less and less indicated. During the past five years it has been necessary to have gastro-enterostomy performed in only two patients, in one of whom with extensive ulceration near the pyloric ring it was difficult to secure cooperation in the medical cure; in the other the operation was advised and performed on a young man in the ward for long-standing hematemesis, which seemingly

could not be controlled. At the operation no ulcer was found nor could the bleeding point be located. The end-result in both instances was satisfactory.

In brief, while the short loop posterior gastro-enterostomy has given good results in securing relief from the symptoms present in ulcer, no adequate method of pyloric closure has yet been devised which prevents the food from passing through the pylorus after the ulcer has healed. The operation has merely given more adequate drainage and diverted the stomach contents from the ulcer area until healing has taken place. The tendency to heal is always in evidence and will occur in most instances if constant irritation of the ulcer by acid chyme is prevented. The opinion may be ventured that the operation would be far less popular if it was generally realized that by medical means the same results might be secured. This refers as well to the so-called obstructive types, in which, under the management here emphasized, the pyloric opening has increased as the spasm decreased. In the past it is safe to say that the operation of gastro-enterostomy has been frequently performed without adequate prior trial of dietetic and medical measures founded on principles now well established. From the viewpoint of the physiologic principles involved should operative means be indicated, excision of the ulcer and pyloroplasty has more to commend it and will probably in the future be the method of choice.

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ABSTRACT OF DISCUSSION

DR. SAMUEL JAMES MELTZER, New York: I have dealt with the question of sensation of the abdominal viscera at various times. I have taken an interest in two questions. One was concerning the sensation of pain in the abdominal viscera in general. Lennander and other surgeons have put up the claim that the visceral peritoneum possesses no nerve fibers for pain. It is a fact that when the abdominal cavity is opened under cocain anesthesia, the viscera can be manipulated without producing any pain to the conscious patient.

We have explained this fact in two ways. In the first place, that in all these cases cocain was used, and we discovered that cocain may have even a distant analgetic effect. In the second place we have tried to show experimentally that the mere opening of the abdominal cavity is capable of greatly reducing the sensibility of the viscera. The opening of the abdominal cavity also exerts a profound influence on the motility; it stops all peristaltic movements; it exerts further also an inhibitory effect on trophic functions. This is illustrated by the well-known fact that the mere incision of the abdominal cavity is capable of curing tuberculous peritonitis. I would remind of the further fact that exposure of the brain or of the cord is capable of abolition of sensation of these organs. My second interest was concerned with the nature of pain in colic. My interpretation of it was based on the so-called "law of the intestines." When any place of the intestines is stimulated it produces a contraction above and a relaxation below. That is the normal effect of a stimulus. However, in an abnormal state, it may occur that a stimulation may cause simultaneously a strong peristaltic contraction above and a constriction below the stimulus. The progress of the peristalsis downward has the effect that the same mass, fluid and gas, would have to find place in a smaller volume; hence the colic. I applied the same explanation to gastric colic. It may occur when the strong contraction of the pre-antrum is progressing forward, while the pylorus remains strongly constricted.

DR. MILTON HOWARD FUSSELL, Philadelphia: There is no easier problem to be solved than the relief of symptoms of duodenal and gastric ulcer. Take a case of gastric or duodenal ulcer, whether acute or chronic, and place that patient on Lenhartz treatment, or the treatment that has been suggested here, or on any of the accepted medical forms of treatment, and in a very short time the patient will be relieved of the pain. He will soon gain in weight and apparently he will be cured. But simply to attack and relieve the symptoms and say then the patient is cured is a great error. I believe the medical treatment of acute peptic ulcer has its place and every case should be so treated. But I also believe that the chronic ulcers should not be so treated. Operations now are much more valuable in chronic ulcers than is medical treatment. The statistics published by the Mayos, Deaver, and others, show that hour-glass contractions, perforation, hemorrhage and carcinoma are much less common in those cases that are treated surgically, and the end results are much more frequently cures than are the results of medical treatment. I have therefore come to the conclusion that every individual who has a chronic gastric or duodenal ulcer is no longer a medical but a surgical case and should be treated by a skilled surgeon. When the operation is done I believe that patient is out of danger from carcinoma, particularly if it

is a chronic gastric ulcer. This cannot be said of the medical treatment of chronic ulcers.

DR. ANTHONY BASSLER, New York: Since about one half of the cases of gastro-duodenal ulcers have a subnormal or absent acidity, then the pain is motor rather than sensory; thus I think the points raised are well taken. On this basis the relief of the subjective symptoms, by lowering peristalsis with alkalies, should prove of value. Also, when an excision of the ulcer, or a gastroenterostomy is done, there is a distinct lessening of the motility of the stomach for a time. There is an interference accomplished by the operation which causes a lowered status of motility. I am not arguing in opposition of drainage, as a factor in operation, but in favor of relief of pain. Without wishing to criticize the carbohydrate diet in a personal way I believe that the benefits accomplished in hyperacidity or in ulcer are not so much due to any restriction of the carbohydrates as to the restriction of all food constituents. It makes little difference whether we restrict the proteins or the carbohydrates. The main thing is that the majority of hyperacidity patients eat themselves into hyperacidity, leaving out the neurologic and psychologic cases. The restriction of carbohydrate and the normal amount or lesser amount of proteid makes little difference in the end. The main thing is that the diet should only be equal to the patient's individual necessities, and it is not necessary to weigh the food to accomplish this in every case.

DR. J. W. DRAPER, New York: The question of operation in these cases, from the surgical standpoint is by no means decided. We have recently experimented on a large number of animals, trying to find the cause of this impairment. Dr. Barber has shown that if a segmental resection of the stomach is made, the function afterward remains practically perfect. Whereas, if a V-shaped piece is removed the function is impaired. There is another point of great interest, the differential diagnosis between duodenal and gastric ulcer. Carcinoma never follows ulcer of the duodenum but it does frequently follow ulcer of the stomach. It is not known why this is so. Hyperchlorhydria is an interesting subject. It has appeared to us from a study of the biologic side that this may be a protective factor by which the organism attempts to prevent aggressions of different kinds. It is unquestionably a symptom.

DR. ISIDOR TUMPOWSKY, Chicago: The "law of the intestines" supports our conception of gastric pain, i. e., when the part above contracts and the part below fails to relax pain results. When gastric peristalsis occurs and the pylorus fails to relax either from spasm or deficient neutralization of the excessive acid passed into the duodenum, pain results from increased intragastric tension. The pain is accompanied by contractions. Pain is not felt unless contractions are present. In the quiescent periods pain is not registered. This

seems to point to the conclusion that tension is the cause of the gastric pain.

DR. WILLARD J. STONE, Toledo, Ohio: I believe it is up to the surgeon who advocates gastroenterostomy without appropriate prior medical treatment to prove that there is no impairment of stomach function after this operation. The vast majority of gastric and duodenal ulcers are amenable to medical treatment by the methods outlined by Sippy and Lenhartz or by the plan here suggested. If, a reasonable length of time after the so-called medical cure has taken place with the patient free from symptoms, there is a recurrence, we may then consider the possible necessity of operative procedures. The point I wish to make is that many gastroenterostomies are being performed today without efficient prior medical treatment.

SYPHILIS AS A PROBABLE FACTOR IN VAGUE STOMACH DISORDERS

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Hospital and private case records show stomach troubles as the chief or presenting symptom in a very large percentage of all patients. In many others, while not the chief complaint, it figures prominently in the chronicle of their troubles.

The former presumption of guilt on the part of the complaining stomach led to many fine-spun diagnoses to fit elaborate classifications. The more recent view of innocence on the part of the stomach until guilt is proved, makes for greater thoroughness in the search for causes of symptoms both intragastric and extragastric.

It is not difficult to understand why the stomach protests so frequently and so emphatically against disturbances originating outside itself when we recall the embryologic relation of the whole alimentary apparatus with its common innervation by branches of the vagus and great sympathetic abdominal plexus.

This provides a mechanism so marvelously delicate as to respond to the slightest stimulus either psychic or somatic, for example, the sight or odor of appetizing food producing gastric secretions or the reflex irritation of a chronic appendix causing regurgitation of food.

The problem of determining and separating the two classes, those in which the lesion is in the stomach (organic) and those in which this organ suffers reflexly or vicariously (functional), has been greatly simplified by improvement in diagnostic methods in general, enabling the more certain recognition of all

extragastric diseases. But of far greater value have been the roentgenologic studies of the gastro-intestinal tract and of surgical pathology after exploratory laparotomy.

Notwithstanding these methods for thorough sifting, there is still too large a class of so-called functional diseases of the stomach which in reality is made up largely of sufferers from visceroptosis, pyogenic infections, early myocardial or valvular disease, hyperthyroidism, latent tuberculosis and syphilis.

There is a rapidly growing literature of organic syphilis of the stomach, diagnoses now being based on positive clinical Roentgen-ray and serologic findings, in spite of the contention of pathologists that the disease is rarely demonstrable in tissue examinations after operation or post mortem.

The acceptance as bona fide gastric syphilis of cases in recent reports by Smithies twenty-six cases, Esterman twenty-one cases, Downes and LeWald eight cases, Morgan seven cases, all based on clinical, Roentgen-ray and serologic findings will lead us to expect from other workers a great many cases of the same character. On the other hand, fewer could be accepted as undisputed stomach syphilis, if all cases were to conform to the requirements laid down by Chase, namely, a positive Wassermann, evidence of syphilis elsewhere in the body, demonstration of lesions in the stomach by Roentgen ray, and finally, therapeutic improvement.

A question of great theoretical interest as well as practical importance is how we shall classify cases which meet only the first and last of these requirements, that is, those with stomach disorders showing positive Wassermanns in which all symptoms are relieved by antisyphilitic treatment.

In the light of the newer pathology syphilis may be said to affect the stomach in some one or all of the following ways: (1) by producing gumma, erosion or endarteritis in the organ itself; (2) by causing demon-

strable structural changes in other organs closely situated anatomically or allied in function to the stomach; (3) by producing changes not recognizable histologically, but due to spirochetal action direct, or through the agency of its toxins on the stomach itself, on the general nervous system, or on the blood.

In the case of the first two groups, that is cases in which gross structural changes are presented, the striking and urgent character of the symptoms and physical findings usually lead to the employment of the Roentgen ray, the Wassermann reaction and often to surgical operation. The very gravity of the symptoms is the salvation of these patients.

Unfortunately the third group of cases, showing no gross changes in organs, presents manifestations of such mild and varied character, often in so many different parts of the body, that the stomach symptoms may at times be obscured by other features and the general impression of nervous instability leads one to brand the patient as neurotic or as having nervous dyspepsia. Boas says:

> By nervous dyspepsia the authors who have paid special attention to this subject, Von Leube, Stiller and Ewald, understand a variety of conditions. Nervous dyspepsia is not a disease but a symptom complex in which organic changes connected directly with the digestive organs may be detected or absent.

The idea of syphilis as a cause of functional gastric disorders is by no means new, as evidenced by many older textbook statements; for example, Hyde, so long ago as 1888, said: "It should not be forgotten that a long list of functional disorders of the alimentary canal might be enumerated as of occurrence in the syphilitic subject which are often due to the toxic influence of the disease (cachexia, etc.)"

Before the discovery of the spirochete and the complement fixation test, the diagnosis of syphilis as a cause of these disorders rested on the history, with its usual denial of infection, on very uncertain physical evidences and finally on the therapeutic test. Since

the discovery of these most positive evidences we have been compelled to acknowledge the disease as exceedingly common in all grades of society and very often nonvenereal in the method of its acquirement. Though still "visited as an iniquity of the fathers upon the children," it no longer carries the moral damnation of original sin.

This radical change in mental or moral attitude toward syphilis has put medicine forward a tremendous stride. As matters now stand, the demonstration of the presence of active syphilis depends on obtaining a positive Wassermann reaction on the blood or spinal fluid, and hence the performing of routine tests on all medical cases, especially those with stomach symptoms, becomes most desirable. A few statistics of such examinations from recent literature offer some variable but suggestive results. Horner in 500 cases finds positive 13.8 per cent., Moore in 418 cases finds positive 13.4 per cent., Edsall in 1,696 cases finds positive 9.4 per cent., and forty-six of these latter had gastro-intestinal symptoms.

In the discussion of his figures Edsall remarks that "the most striking fact brought out is the much greater frequency of gastro-intestinal manifestations (not gastro-intestinal syphilis) than we have thought till recent years."

The group of vague gastric disorders in which syphilis is believed to be concerned is largely made up of congenital cases lacking the classical picture of the disease and hence unrecognized and untreated; congenital or acquired cases suspected and insufficiently treated; and acquired often nonvenereal syphilis, of a mild type because of a weak strain of infecting organism or unusual resistance of the patient. All of these types were formerly called merely latent syphilis.

Since Warthin finds spirochetes in cardiac muscle as well as in other organs which show no lesion, "which according to the older knowledge would be classed as syphilitic," we may accept his theory for the periods

of latency in persons who, though free from symptoms for decades, show abundant organisms in their tissues. He assumes that a symbiotic relation exists between the organisms and the body cells.

This view accords with the conclusions of Nichols and Hough, from experimental data that "syphilis is not to be thought of as a chronic septicemia extending over years, but rather a complex of local infections which date back to an early septicemia and the character (strain) of spirochete eventually determines the picture of the disease."

This view of latency, as symbiosis, would explain more satisfactorily such phenomena as the late (parasyphilitic) manifestations and the negative complement fixation test which becomes positive after provocative doses of antisyphilitic remedies. As to the exact method by which gastric symptoms are produced in syphilis without demonstrable lesions of the stomach we can at present only speculate. If we exclude from consideration cases with definite lesions of the central nervous system, two ways seem possible either by the actual localization of spirochetes in the stomach or through absorption and circulation of toxins in the blood. This latter would seem analogous to the early gastric disorders seen in pulmonary tuberculosis, in which no lesion of the stomach exists.

A vast amount of work must yet be done to clear up the pathology of syphilis and establish the Wassermann, luetin and various spinal fluid tests on an entirely satisfactory basis. But the application of our present knowledge is revolutionizing internal medicine and enabling us to save many syphilitic gastric patients from years of unnecessary suffering, surgical tampering or even worse fates.

Herewith are appended case reports believed to be illustrative of some of the types discussed.

CASE 1.—White, married man, 36 years old, complained that for five weeks he had had "stomach trouble" nearly continuously. From three to four hours after a meal, especially if

he had exercised much, he felt a considerable pain in his stomach. This pain remained localized, not radiating, and was relieved on taking any sort of food. He believes the pain was worse after a heavy than after a light meal. He did not vomit, nor did he have heart burn or eructations. The bowels were somewhat constipated. His weight was off from 12 to 15 pounds.

His trouble was diagnosed as syphilitic gastric dyspepsia and progressive tabes.

The history shows that this man has had a facial paralysis for nine years and that he had something like syphilis a few weeks preceding its development. The treatment he received was the usual hot springs vacation with very casual dosing for a few weeks with a liquid containing mercury and potassium iodid.

About one year later, or Sept. 25, 1907, he consulted me because of pain and fulness in his stomach, coming on an hour or two after eating. His bowels were regular. He had lost 25 pounds in a year.

Examination then showed right-side facial palsy, negative heart, lungs and abdominal viscera, urine containing a few hyaline and granular casts. The blood was negative to ordinary tests, the Wassermann not being then in vogue.

Examination of stomach contents, which was then very much in vogue, showed after an ordinary Ewald meal total contents 90 c.c., hydrochloric acid 16, total acid 25. From these findings it was thought that no serious stomach disorder was present, in other words, our old friend, "neurosis or purely functional" was chosen for a diagnosis, and the patient was advised to feed up and renew his antisyphilitic treatment and report in ten days. He was not seen again till 1910, three years later, when he was much improved, but still had his facial paralysis.

A few weeks ago he returned complaining that for five weeks he had pain after meals, as already described. The periodicity and general character suggested duodenal ulcer, but there being no demonstrable blood in the stools and no abdominal tenderness, this diagnosis was held in abeyance.

He was found to have delayed right patella reflex and slight Romberg. The Wassermann reaction was three plus positive. Examination of eye grounds and auditory nerves preliminary to giving salvarsan was made and it showed defective hearing in both right and left ears and marked arteriosclerotic optic disk.

In view of these changes and the risk involved in large dosage of arsenic, we decided on slower treatment, and accordingly he was given mercury salicylate intramuscularly with increasing doses of potassium iodid. Following marked improvement in the eye and ear conditions, he was later given arsenobenzol.

No direct attention has been paid to the stomach disorder except for some suggestions as to diet and laxatives. The improvement in the patient has been very marked, the stomach symptoms having entirely cleared up and though he still has a long way to travel, I hope the syphilitic condition may be arrested and further damage to the gastro-intestinal tract and nervous system be averted.

CASE 2.—American woman, married, 33 years old, presented as the principal complaint these facts: For about four or five months had had severe pain in the stomach region and also in the right thorax. She had a feeling of "rawness and soreness" in the stomach and suffered from nausea and vomiting when the stomach was empty. She had on two occasions vomited blood, which was at one time bright red and at another dark, there being 1 to 2 ounces each time. A week before she had passed some pus and blood in the stool. She had a poor appetite and was constipated. Having lost 20 pounds and much strength, she was bedridden and greatly depressed mentally. Another condition which was thought possibly to have some relation to the stomach trouble was excessive uterine flow at times, both metrorrhagia and menorrhagia, with moderate leukorrhea.

Her case was diagnosed as stomach ulcer, probably gumma.

Some other points of interest in the history are that she had pneumonia followed by pleurisy thirteen years before and mild attacks of pleurisy every winter following. Up to six years before she also had bronchitis every winter. She had one living child and no history of miscarriages. Her husband is in excellent health, having no suspicion of syphilis.

The examination shows a thin anemic woman with signs of old pleurisy at the right base, a very tender resisting area in the left upper abdomen above and to left of the umbilicus, in other words about over the stomach.

She has a moderate secondary anemia with hemoglobin 55, 4,600,000 red cells, 5,500 white, blood pressure 108 and 80 mm. of mercury, urine negative, stool with no occult blood and no ova.

The examination of the uterus showed an enlargement of this organ with an eroded, easily bleeding cervix and a small mass in the posterior cervical lip.

The general picture here presented suggested strongly carcinoma of the uterus with probable metastasis in the gastro-intestinal tract. The patient was seen by Dr. L. H. Watkins, who diagnosed an acute endocervicitis. It was decided to take her to the hospital and examine the cervix further, making a microscopic examination of the tissue, and study further the stomach condition by means of the Roentgen ray.

The Roentgen ray showed both with fluoroscope and plate a definite lesion (probable ulcer) on the lesser curvature immediately beneath the tenderest point on the abdomen. The

characteristic incisura in the greater curvature directly opposite was also noted with a stoppage of the bismuth and with a ragged appearance at the point of suspected ulceration.

Further examination of the uterine condition by Dr. Watkins confirmed the diagnosis of endocervicitis, probably of Neisser type. The Wassermann reactions, made by two careful observers independently, were both positive, three plus.

The usual ulcer diet and regimen were instituted and a few days later the patient was given 0.6 gm. of salvarsan. She has since been on mercury by intramuscular injections and potassium iodid. Some little attention has of course been paid to diet, laxatives and medication, but the marked and prompt improvement noted and which is continuing both in the behavior of the stomach and in the general condition, together with a gain of 40 pounds in weight and a clearing up of the anemia, we believe has been largely due to antisyphilitic treatment.

CASE 3.—An American mechanic, 27 years old, had stomach trouble, weakness and "generally down-and-out feeling for three or four years." He felt so bad that he was unable to work except a day or two a week.

Three years before, after much treatment by different doctors, the inevitable happened, his appendix was removed by a surgeon who told him it was chronically inflamed and was the cause of all his digestive disturbance.

The symptom complained of at that time and which persisted after his separation from his appendix were heaviness in the epigastrium, with much distention with gas, constipation and dizziness. On careful inquiry into the history it was found that he had a definite, typical syphilitic infection in 1907, just eight years before. Following this he took about six months' internal treatment. Again three years before he took salvarsan intravenously. Up to the time of examination there had been no particular change in the gastro-intestinal or general condition.

This patient was sent to the hospital May 24, 1915, for study, and it was found on Roentgen-ray examination that, aside from a redundant sigmoid, there was no pathologic condition present in the alimentary tract, the stomach itself being absolutely normal.

A diagnosis of syphilitic gastric dyspepsia was made.

A Wassermann reaction made on entrance showed moderately positive, two plus. The blood findings aside from this were not striking. The urine, blood pressure and general physical examination were negative. The stool showed no occult blood. No gastric analysis was made.

On May 31, 1915, the patient was given salvarsan and a week later intramuscular injections of mercury were begun, followed in the intervals with potassium iodid. This man has now been under observation more than a year and is quite well of his stomach trouble.

SYPHILIS IN THE SOUTHERN NEGRO*

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The question of the prevalence of syphilis among the negroes of the South has, until recently, been the subject of much discussion and conjecture, but of little scientific investigation.

It is the belief of the majority of physicians working among the negroes in the South that a great percentage of them are syphilitic.[1] On the other hand, it is the belief of other clinicians, working among a better class of negroes, especially in the North, that such an estimate is not correct.[2] Most of these estimates, however, are based solely on clinical observations and not on systematic and strictly scientific investigations.

The results of the few systematic attempts at the solution of this question regarding the prevalence of syphilis among the negro population of the South have been somewhat contradictory. Hindman[3] has reported 16 per cent. of infections as determined by routine Wassermann reactions, among 255 male negroes and the same percentage among 218 female negroes incarcerated in the Georgia Insane Asylum. Ivey[4] reports 25 per cent. of 357 male insane negroes, and 29 per cent. of 349 female insane, as having positive Wassermann reactions, at the Mt. Vernon Insane Asylum,

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1. Murrell, Thomas W., discussion on Kingsbury, Jerome, and Brecht, Paul E.: The Intravenous Administration of Mercury in Syphilis, THE JOURNAL A. M. A., Aug. 15, 1914, p. 565. Martin: South. Med. Jour., 1914, vii, 466. Terry: South. Med. Jour., 1914, vii, 458.
2. Hazen, H. H.: Syphilis in the American Negro, THE JOURNAL A. M. A., Aug. 8, 1914, p. 463.
3. Hindman: Am. Jour. Pub. Health, 1915, v, 218.
4. Ivey: Med. Rec., New York, 1913, lxxxiv, 712.

of Alabama. Lynch[5] reports 65 per cent. of negro women, and 53 per cent. of negro men, applying at the outclinics of Charleston, S. C., for treatment, as having positive Wassermann reactions. Unfortunately, however, Lynch's series of tests is limited to only 102 in all. Wilson,[6] in a series of tests done on seventy-six healthy negro girls in an orphan asylum of Baltimore, found 7.8 per cent. to have a strongly positive Wassermann reaction.

As a result of this very decided variation in the figures of various observers, it has seemed to us that a systematic and more or less extensive series of observations as to the prevalence of syphilis among the negroes would not be out of place.

The work which we are to report was carried out on negroes in the city of Galveston. The majority of the negroes examined were of the laboring class, being for the most part dockworkers, longshoremen, sailors and common laborers, with their wives and families.

The reactions which we have employed in the attempt to detect syphilitic infection were the Wassermann and luetin tests. The Wassermann tests were done after the modification of Noguchi, using liquid reagents, however, instead of paper. The luetin tests were done in the ordinary manner, 0.07 c.c. being given intradermally. All tests were carried out in the medical clinics and laboratories of the University of Texas, Department of Medicine; the blood of each negro admitted to the wards of the John Sealy Hospital, regardless of service to which admitted, being taken as soon after admission as possible and the luetin reaction being given at the time the blood was taken. No Wassermann or luetin reaction was considered positive unless the reaction was an undoubted positive, doubtful reactions being considered negative. Only Wassermann reactions of one plus (50 per cent.) or more fixation were considered

5. Lynch: South. Med. Jour., 1915, viii, 450.
6. Wilson: New York Med. Jour., 1916, ciii, 585.

positive, the classification of Craig being used.[7] All tests were done in the same laboratory and interpreted by the same observer.

The series which we have examined in the above manner consists of about 1,200 adult negroes, fifteen years of age or over. On 600 of these negroes both the Wassermann and luetin reactions could be successfully followed, while in the remaining 600, only the Wassermann reaction could be obtained. Among

OCCURRENCE OF SYPHILIS IN THE COMMONER DISEASES, AS DETERMINED BY POSITIVE WASSERMANN REACTIONS ON THE NEGRO

Disease	No. Cases	Per Cent. Positive Wassermann
Apparently healthy adult negroes	200	24
Negro children	52	9.5
Pulmonary tuberculosis	60	23
Typhoid	13	22
Malaria	7	12
Dysentery (amebic and bacterial)	12	20
Pneumonia	30	30
Pellagra	22	13
Cancer	17	12
Arteriosclerosis (or senility)	18	23
Chronic interstitial nephritis	4	25
Diffuse nephritis (often subacute or acute)	60	48
Paralysis	34	50
Myocarditis (uncomplicated by organic valvular lesions or by nephritis)	21	40
Cirrhosis of liver	6	66
Aneurysm of thoracic aorta	12	83
Aortic insufficiency	20	75
Syphilitic bone or joint pains	30	80
Rectal abscess	4	75
Rectal stricture	10	90
Rectal fistula	13	61
Hemorrhoids	9	22
Chronic leg ulcer	18	55

the latter 600 patients, however, are included all those on whom luetin reactions were done, but who disappeared from view before the reaction could be satisfactorily interpreted. Also among these patients are included all those having had potassium iodid in any amount before the interpretation of the luetin test, for there seems to be no doubt, in our experience, that a positive luetin can be produced at will on non-syphilitic individuals, by the previous administration of the iodids in sufficient quantities.

7. Craig: Am. Jour. Med. Sc., 1915, cxlix, 41.

Of the 1,200 negroes examined in this manner, 34 per cent. gave definite positive Wassermann reactions. Of the 600 negroes on whom both Wassermann and luetin reactions were done, 35 per cent. gave definitely positive Wassermanns, and 18 per cent. gave positive luetins, while the total percentage giving positive reactions to one or both of these tests was 42 per cent., 7 per cent. giving positive luetins with negative Wassermanns. Such statistics as these are of comparatively little real value, however, in arriving at a true idea as to the actual prevalence of syphilis among a race of people. It is a well-known fact that the percentage of syphilis among patients applying to clinics for treatment is always much higher than among the healthy working classes, so that, before drawing any conclusions as to the actual prevalence of this disease, as well as its actual relation to sickness and death, it becomes necessary to determine the percentage of healthy and robust negroes who are infected with syphilis.

In order to determine, therefore, the actual prevalence of syphilitic infection in the healthy working negro, we have made an especial study of some 200 such persons. Among these are included all negroes admitted to the surgical wards of the hospital, suffering from accidental injuries, such as broken legs, cuts, stab wounds, burns, etc. Particular care was taken in selecting these negroes to rule out all who were otherwise diseased or disabled than from their injury. Along with these cases were included, also, a small number of normal obstetric cases. Of these various, apparently normal cases, 24 per cent., approximately, gave positive Wassermann reactions, 12 per cent. gave positive luetin reactions and 28 per cent. gave positive reactions to either the Wassermann or the luetin tests.

In order to determine, moreover, what percentage of syphilis might be hereditary among the negroes and what acquired, we attempted a very limited study of

negro children, ranging in age from 1 year to 12 years, in whom it was presumed that any syphilitic infection must be inherited. These children were, however, admitted to the hospital complaining of some ailment, either medical or surgical, so that the figures which we have obtained are probably somewhat higher than would be met with among absolutely healthy negro children. They are sufficient, however, to show that the majority of the cases of syphilis among the negroes are of the acquired type, nature, fortunately, taking care of many of the patients with inherited syphilis by affording them an easy death either before or immediately after birth, as well as by rendering the parents sterile. Of fifty-two such examinations which we have made, we found only five positive Wassermann reactions, giving a percentage of about 9.5. In addition, however, one patient had positive luetin reaction with a negative Wassermann, making the percentage slightly higher.

Of greatest interest to us, as clinicians, was the study and analysis of the incidence of positive Wassermann and luetin reactions among patients suffering from the various common diseases. This subject we hope to take up in more detail in a paper to be read elsewhere, but a brief summary of our findings would, perhaps, not be inappropriate here.

Taking up first the purely medical cases, cases admitted to the medical wards of the hospital, we find that we have some 400 in our series. Of these, about 40 per cent. gave definitely positive Wassermann reactions. Adding to this percentage those cases which gave positive luetin reactions with negative or doubtful Wassermann reactions (twenty-one cases), we have a total of 45 per cent. giving strong laboratory evidence of the existence of syphilis. Analyzing the incidence of positive reactions in the various common diseases, we find that such diseases can be readily grouped into three divisions, from the standpoint of syphilitic infection. First, we have those diseases which seem to

have no direct connection with syphilitic infection, since the incidence of positive reactions in these is remarkably constant, ranging always somewhere around that percentage which we have found to be usual in healthy negroes. Next, there is a group of diseases in which the incidence of positive reactions is somewhat higher, suggesting that while perhaps syphilis is not a direct cause of the disease, or at least not the sole cause, nevertheless, syphilitic infection must be a contributing factor toward its occurrence. Finally, we have certain diseases in which we have learned to predict a positive reaction in almost every instance, diseases which are certainly caused by previous syphilitic infection.

Among the first group of diseases, which, apparently, have no connection, either direct or indirect, with syphilis, and comprising some 200 cases in all, we find the following diseases, all showing an incidence of positive Wassermann reactions of somewhere around 30 per cent.: pulmonary tuberculosis, sixty cases, with 23 per cent. positive Wassermann reactions; typhoid fever, thirteen cases, 22 per cent. positive Wassermann reactions; malaria, seven cases, 12 per cent. positive Wassermann reactions; pneumonia, thirty cases, 30 per cent. positive Wassermann reactions; dysentery, twelve cases, 20 per cent. positive Wassermann reactions; pellagra, twenty-two cases, 13 per cent. positive Wassermann reactions; cancer, 17 cases, 12 per cent. positive Wassermann reactions; chronic interstitial nephritis, four cases, 25 per cent. positive Wassermann reactions, and arteriosclerosis, eighteen cases, 23 per cent. positive Wassermann reactions.

Still other diseases, mentioned above as perhaps indirectly associated with previous syphilitic infection, have shown constantly a rather higher percentage of positive reactions than we have learned to consider normal for the negro. The most striking type of disease of this second class is a form of diffuse nephritis

to which the negro of these parts seems peculiarly susceptible. We are, all of us who work in the South, acquainted with the common "dropsy," which is so well known to the darkies themselves. This disease is manifested clinically by a massive anasarca, by dyspnea, by cardiac irregularities, hypertrophy and dilatation. Usually the disease is rather rapid in its course. Pathologically, an acute or subacute diffuse nephritis is usually found, involving as a rule both glomerular and tubular elements of the kidneys. Excluding all cases of pure chronic interstitial nephritis and all cases of renal sclerosis, we have studied sixty cases of this diffuse nephritis. Of these, twenty-five gave negative reactions, twenty-four gave positive reactions, and eleven gave doubtful reactions. Of the latter giving doubtful reactions, five gave positive luetin reactions, making twenty-nine cases in all giving positive reactions to one of these tests, a percentage of 48 per cent. positives as against only 40 per cent. clear-cut negatives.

Still another affection common to the negroes, as all who work among them are aware, is a spastic paralysis or paresis, occurring especially in young or middle-aged negroes, often of one limb or group of muscles, but still more frequently, perhaps, involving more than one group. A certain number of such cases are, of course, purely arteriosclerotic in origin, but that a large percentage of them are syphilitic is shown from the fact that out of thirty-four of such patients studied in this series, 50 per cent. gave positive Wassermann reactions. The majority of those giving positive Wassermann reactions, moreover, gave positive reactions in the spinal fluid also.

Another disease which would seem to be connected with syphilitic infection in some way, although not certainly caused solely by that infection, is myocarditis. From this group we have excluded as far as possible all cases of myocarditis complicated by valvular lesions of an organic nature, also all cases complicated

by nephritis. Twenty-one such cases were observed. Of these, eight, or 40 per cent., gave positive Wassermann reactions, three, or about 10 per cent., were doubtful, and 50 per cent. were negative.

Cirrhosis of the liver, usually, among the negroes, consisting of a large, hard and tender liver, would seem to be largely specific in origin, since out of six cases observed, four gave strongly positive Wassermann reactions.

Of the third type of disease common among the negroes, but which is almost constantly associated with a positive Wassermann reaction, aneurysm of the thoracic aorta is a good example. Of twelve such cases in this series, ten gave definitely positive reactions, one gave a doubtful and one a negative reaction. Three cases of abdominal aneurysm were studied. Only one of these gave a positive Wassermann reaction. Two were negative both to Wassermann and luetin reactions. One carotid aneurysm gave a positive reaction, one femoral a negative, and one iliac a negative reaction.

Twenty cases of aortic insufficiency were observed in this series. Fifteen of these, 75 per cent., gave positive Wassermann reactions and 85 per cent. gave positive reactions to either Wassermann or luetin tests.

One other disease stands out prominently among the medical cases as being commonly associated with positive reactions for syphilis. This is a mild type of bone pain, usually called rheumatism or lumbago by the sufferer, characterized clinically by bone or joint pains, without, however, any redness, swelling or deformity. There is usually no rise ot temperature. A very characteristic point in the history is the fact that the pains are usually worse at night. Headache is apt to be a complication. Joints are especially apt to be affected, although the long bones are not infrequently involved, as well as the ribs, spine and skull. Local tenderness is not marked as a rule. Such cases are exceedingly common in our clinics, especially in the outclinics. Of

thirty such cases studied, twenty-five, or about 80 per cent., gave strongly positive Wassermann reactions, and 84 per cent. gave either positive Wassermann or positive luetin reactions.

A study of Wassermann reactions done on negroes admitted to the surgical wards of the John Sealy Hospital, about 300 cases in all, shows a lower incidence of positive Wassermann reactions than on the medical wards, only 34 per cent. of these giving positive Wassermann or luetin reactions, as distinguished from 45 per cent. of positive reactions obtained on the medical service. Only three diseases stand out prominently among the surgical cases as being especially associated with positive Wassermann reactions. The most striking of these is the well-known "rectal trouble" of the negro. These rectal troubles are found on investigation to be of five kinds, namely, hemorrhoids, fistula in ano, perirectal abscess, stricture of the rectum and chondromas. With the exception of those patients suffering from hemorrhoids, nine of whom were examined, with an incidence of positive Wassermann reactions of only 22 per cent., all of the remainder of these rectal troubles would seem to be closely connected with syphilitic infection, since out of thirteen patients with rectal fistula, eight, or 61 per cent., gave positive Wassermann reactions; of four with rectal abscesses, three gave strongly positive reactions and one a doubtful reaction; and of ten with strictures of the rectum, nine gave strongly positive Wassermann reactions. It would seem, therefore, that rectal trouble in the negro is strong presumptive evidence of syphilis.

One other surgical disease standing out prominently in our series as being frequently associated with positive Wassermann reactions is the chronic leg ulcer. Out of eighteen such cases, ten gave positive Wassermann reactions (55 per cent.), and one a doubtful reaction. Finally, of seven cases of periostitis observed, three gave strong positive Wassermann reactions, one a doubtful, and three a negative reaction.

Of 200 gynecologic cases examined, 29 per cent. only gave positive Wassermann reactions. Among the gynecologic cases, no particular disease has been peculiarly associated with positive reactions. Out of thirty-two obstetric cases, ten gave positive Wassermann or luetin reactions, a percentage of 30. Only three miscarriages were observed among these. Two of these miscarriage cases gave positive reactions and one a negative.

In a study such as this one of the prevalence of syphilis in any particular class of individuals dwelling in a community, it is of course important to determine, if possible, the incidence of the same infection among the other classes of the same community. Such a determination among the white patients admitted to the wards of the John Sealy Hospital, in a limited number of cases only, however, has been done. Before reporting the results of this investigation it would perhaps be well to say a few words in explanation of the class of white people on which this work was done. We treat in the wards of the John Sealy Hospital two entirely different classes of persons. On the one hand, many are small shopkeepers, farmers from the surrounding territory, clerks, tradesmen, etc. On the other hand, a large number are of the so-called lower classes, including sailors, longshoremen, common laborers, and, finally, the human derelicts or the dregs of social life.

The incidence of syphilitic infection among the better classes of these patients, taken as a routine on admission, would seem to be considerably lower than that among the negroes, averaging somewhere about 20 per cent. (fifty cases only). On the other hand, the incidence among the latter class of patients, those at the bottom of the social scale, differs very slightly from the incidence found among the negroes of the same class, averaging about 30 per cent. (fifty cases).

Finally, in a series of Wassermann tests done on about fifty healthy medical students, the tests being done in a routine manner, without selection, we have not yet found a definitely positive reaction.

CONCLUSIONS

The conclusions which we feel that we can draw from this work are as follows:

1. The incidence of syphilitic infection among apparently healthy adult negroes in this community varies between 25 per cent and 30 per cent.

2. The infection is largely acquired, since it is much lower in incidence among children under the age of puberty.

3. The incidence of syphilitic infection among sick negroes is considerably higher than among the well, averaging between 40 per cent. and 50 per cent.

4. Certain diseases seem to be directly connected with previous syphilitic infection, as shown by extremely high incidence of positive reactions. In other diseases, moreover, syphilis, although apparently not being the direct, or at least the sole cause of the disease, would seem to be connected with its occurrence in some way, chief among these being the characteristic form of acute or subacute diffuse nephritis, which is one of the most common causes of death among the negroes.

5. The occurrence of syphilis among white people of the same social class as the negroes would seem to be about the same as that among the negroes. In the better classes of white people, however, the occurrence is much less, while in the best classes (young and healthy medical students), it is almost nil.

6. Syphilis is undoubtedly one of the chief causes of death and disease among the negro, ranking as high or higher than tuberculosis, Bright's disease and pellagra, which are the three other chief causes of death and disability among that race in this community.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. LULL AND M'NEIL

DR. FRANK SMITHIES, Chicago: The subject of visceral syphilis is in evolution. The earlier pathologic studies are incomplete. Dr. Warthin of Ann Arbor has demonstrated in the pancreas lesions similar to those found in the aorta and myocardium. He also demonstrated spirochetes in the pancreas parenchyma. It would seem that we must cease to regard syphilis as a dermatologic ailment but consider it broadly as a spirochetemia. We cannot state that the syphilitic virus, the spirochete, does not lodge in the wall of the stomach or other hollow viscera. It is extremely likely that it does. Its lodgment there is probably delayed on account of the active motility of the stomach, and added vascular protection. We should not wait for the development of a tumor or malformation before classing lesions as syphilitic. Such are terminal affairs. In all cases of chronic dyspepsia one should make a Wassermann test not only of the blood serum but of the spinal fluid as well. A positive reaction should always be confirmed by a second test. We do not think that the luetin test is a reliable clinical guide as to the presence or absence of syphilis. If one approaches the subject of visceral syphilis from this standpoint he will be surprised at the comparatively large number of cases that come in diagnosed "dyspepsia" which will reveal some venereal history which has been forgotten or hidden and in which positive serum tests are obtained. In some instances the disease may be congenital. In syphilitic cases the clinical manifestations are very similar to those of dyspepsia from other gastric lesions. One should not wait until tumor deforms the stomach before suspecting syphilis. When tumor has developed it indicates the end of the story. Gastritis, ulceration or cirrhosis usually precede tumor formation.

Reports of great improvement following specific treatment of lesions which are considered syphilitic should be considered conservatively. In 80 per cent. of chronic ulceration of the stomach, especially in syphilitic ulcers, there is a history of intermittency or "periodicity." Favorable intervals often occur whether or not treatment is instituted. Out of 33 cases of visceral syphilis in my series only five can at present be considered clinically well. In seven cases there was no improvement.

DR. FENTON B. TURCK, New York: Gumma of the stomach is an unusual lesion and the number of cases of demonstrable gummas interfering with gastric function is very small. On the other hand, a large number of syphilitics have stomach disorders sometimes of a very distressing sort. In common with other general diseases, syphilis can be manifested by gastric symptoms quite apart from any local syphilitic lesion. Since syphilis is recognized as a spirochetemia, not essen-

tially unlike an invasion of the blood stream by bacteria or plasmodia, the resultant effects are very similar to those of chronic malaria, tuberculosis or low grade systemic infections. Some years ago a physician in Texas made a special report to me on gastric symptoms in chronic malaria. His figures proved the same insufficiency of motility with stasis of stomach contents as is found in tuberculosis and syphilis. The factors responsible for these symptoms are changes in nonstriated muscle as result of direct toxic influence and venous stagnation in splanchnic vessels resulting in an asphyxia of muscle cells and consequent atony. These conditions were found in cases in which no obstruction was demonstrable; the histologic changes were shown in sections from the stomach wall which were taken in attempting operation for relief of gastric symptoms. These microscopic changes were of a hyaline character with a degeneration of muscle cells without infiltration of the gummatous type. Antisyphilitic treatment does not always relieve symptoms secondary to long standing cell poisoning; direct, systematic treatment of the stomach is indicated for reduction of splanchnic congestion and stimulation of gastric motility and secretion.

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